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# ARCHIVES OF DISEASE IN CHILDHOOD



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# MACROCYTIC ANAEMIA IN CHILDREN

## WITH A REPORT OF THREE CASES SHOWING MEGALOBLASTIC ERYTHROPOIESIS

BY

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### General considerations

Anaemias characterized by a macrocytic peripheral blood picture may be divided on the basis of sternal puncture findings into two main groups according to whether the marrow picture is megaloblastic or normoblastic. A **megaloblastic** marrow picture, which is seen in its typical form in relapsed cases of Addisonian pernicious anaemia, may be recognized by the following features (see fig. 1):—

A high proportion of the red cell precursors are large cells with abundant dark-blue cytoplasm and large finely reticulated nuclei in which nucleolar remnants may or may not be present. The nomenclature of these cells continues to arouse considerable controversy, and various names have been given to cell types differentiated from each other by finer points of cytological detail. However, I prefer to designate these cells by the generic name of early erythroblast and support the view that their diagnostic significance lies in their quantity rather than their quality. According to this view the presence in marrow films of occasional cells belonging to the series is of no diagnostic significance since they may occur in small numbers in health and in many types of anaemia, but their presence in relatively large numbers is characteristic of megaloblastic anaemias.

Cells qualitatively diagnostic of megaloblastic erythropoiesis are seen among the more mature red cell precursors showing varying degrees of haemoglobination. Such cells may be identified as megaloblasts by their size and particularly by the loosely woven character of the nuclear chromatin. Normoblasts at equivalent stages of haemoglobination are smaller and have nuclei which are much more dense and lumpy in structure.

In severe untreated megaloblastic anaemias the marrow picture is so characteristic that it is recognizable at a glance. It must be admitted, however, that in mild cases, especially if an iron deficiency is also present, and in cases in which liver therapy has recently been instituted, the diagnosis may not be easy and may necessitate careful study. Indeed, effective liver therapy may result in such a rapid modification of the marrow picture that evidence of megaloblastic erythropoiesis may disappear within a few days of the start of treatment.

A megaloblastic marrow picture is always associated with defective erythropoiesis, the erythrocytes being defective both in quantity and quality, and the presence of numerous macrocytes in the peripheral blood is usually a conspicuous feature.

It should be noted, however, that while the peripheral blood picture is usually hyperchromic, it may occasionally be hypochromic in cases in which a severe iron deficiency is also operating. Trowell (1943) has drawn attention to the relatively frequent occurrence of such ' dimorphic anaemias ' in the tropics; and in Edinburgh this feature has been noted in megaloblastic anaemias of pregnancy. Accordingly it will be seen that a high colour index is not necessarily an accompaniment of macrocytosis, although, in temperate climates at least, it usually is so.

Megaloblastic erythropoiesis is generally considered to result from arrested maturation consequent upon lack of the anti-anaemic, or haematopoietic, principle of Castle. This deficiency most commonly results from defective formation of intrinsic factor as in Addisonian pernicious anaemia. It may also be caused by an inadequate intake of extrinsic factor as in nutritional macrocytic anaemias. Less frequently it may occur in alimentary disorders such as steatorrhoea, sprue, and coeliac disease, which may cause impaired absorption of the haematopoietic principle. Finally, megaloblastic anaemia may occasionally result from diseases of the liver since this organ is the site of storage of the haematopoietic principle, and possibly of its final elaboration (Davidson and Fullerton, 1938).

It is widely recognized that treatment by injections of fractionated liver extracts containing the haematopoietic principle is usually followed by the rapid replacement of the megaloblastic marrow picture by a normoblastic one and subsequent restoration of a normal blood picture.

Occasional cases of megaloblastic anaemia are met with, however, which are permanently or temporarily refractory to treatment with liver extracts. Thus cases of so-called ' achrestic anaemia ' described by Israëls and Wilkinson (1940) were found to be partly or completely refractory to treatment. Davidson, Davis and Innes (1942, 1943) have described refractory cases which responded only to prolonged and intensive parenteral liver therapy. Evidence has been presented by Fullerton (1943), and by Davis and Davidson (1944) in support of the view that in certain cases of megaloblastic anaemia restoration of normal erythropoiesis is dependant upon some factor present in whole liver preparations additional to the haematopoietic principle present in fractionated liver extracts.

Macrocytic anaemias associated with **normoblastic** bone-marrows are occasionally encountered in certain haemolytic syndromes, hypothyroidism, leukaemias, leuco-erythroblastosis and certain types of refractory anaemia. The macrocytic blood picture in some cases in this group is due to large numbers of reticulocytes being present, resulting in a so-called 'pseudo-macrocytosis.' In other cases, however, a true macrocytosis may occur, the mode of production of which is quite obscure.

Since macrocytic anaemias belonging to this group do not ordinarily respond to parenteral liver therapy, the demonstration of such a response in a macrocytic anaemia may be interpreted as presumptive evidence of the anaemia in question being megaloblastic in nature.

Such evidence provided by response to treatment is therefore of importance for the purposes of reviewing published descriptions of anaemic states, since descriptions of sternal marrow biopsies have only recently become commonplace, the majority of published haematological reports are confined to descriptions of the peripheral blood.

In the earlier literature particularly, many cases of macrocytic anaemia have been described as pernicious anaemia on inadequate evidence. For the acceptance of this diagnosis it is desirable that in addition to the characteristic peripheral blood picture, there should be evidence of a histamine-fast achlorhydria, of a prompt response to parenteral liver therapy, and of the absence of possible operating causes, such as tumours or steatorrhoea.

### Macrocytic anaemia in childhood

In childhood macrocytic anaemias have been reported relatively infrequently.

The rarity of pernicious anaemia in the first two decades of life is exemplified by surveys published by the following authors:—Carr (1920); Panton et al. (1923); Wilson and Evans (1924); Montgomery (1926); Davidson and Gulland (1930) and Murphy (1939). Of a total of 1532 cases of pernicious anaemia only four were below the age of twenty years.

A number of individual cases of macrocytic or hyperchromic anaemia during childhood have been reported, but most of these were in infants. Bachman (1936) gave a detailed account of a case of macrocytic anaemia which responded to liver extract in a nine-month-old infant and reviewed previously published reports of ten cases of hyperchromic or pernicious anaemia in infancy. This author considers that all anaemias below the age of one year may be assumed to be nutritional in origin consequent upon such influences as dietary deficiency, defective absorption, vomiting and diarrhoea, or defective storage due to hepatic dysfunction.

Parsons and Hawksley (1933) describe three cases, not referred to by Bachman, of mild hyperchromic anaemia associated with coeliac disease in very young children.

Since Bachman's paper seven further cases in infants have been reported by Langmead and Doniach (1937); Mödlinger (1937); Veeneklass (1940); Cole (1941) and Fouts and Garber (1942). In only one of these, a thirteen-month-old infant, was a histamine-fast achlorhydria recorded. In three of the cases the anaemia was attributed to a diet of goat's milk.

In view of the lability of the haematopoietic system in infancy, the interpretation of haematological findings obviously calls for extreme caution. Accordingly, in infants a diagnosis of pernicious anaemia is justifiable only after rigid criteria have been satisfied. It is doubtful if in any of the published cases have these requirements been fulfilled. In children above the age of infancy, anaemias claimed to be macrocytic in type or to display other resemblances to pernicious anaemia have seldom been reported.

I have succeeded in tracing reports of only sixteen cases, which are published by the following authors. The age of each patient in years is indicated after the relevant reference. Kusonoki (1914)—6; Vischer (1923) two cases—3 and 4; Fanconi (1927) three brothers—4, 5 and 7; Castle (1928)—13; Faber (1928)—4; Eckman and Rowe (1929)—11; Kersley (1935)—11; Adams and McQuarrie (1938)—12; Murphy (1939)—12; Barbé (1939)—2½; Magnusson and Hamne (1939)—8; Templeton (1939)—14; Svastis (1940)—13.

Since bone marrow biopsy studies were not described in connexion with any of these cases it follows that there is no proof that the anaemias were necessarily megaloblastic. Moreover, some of the descriptions of the peripheral blood were inadequate in that they failed to present unequivocal evidence of a genuine macrocytosis, or that the other features of a 'pernicious anaemia-like' blood picture were present.

The results of gastric analysis were stated in respect of seven of the cases and a histamine-fast achlorhydria was found in only four of these. Disease of the alimentary tract was present in three cases (coeliac disease, tuberculosis, megacolon); evidence of pyrexial infection was reported in two further cases and of endocrine dysfunction in another.

A haematopoietic response to parenteral liver therapy occurred in seven of the nine cases in which this treatment was tried. One of these patients remained in good health after liver treatment was stopped. One of the patients who failed to respond to liver therapy made a sustained recovery after a blood transfusion.

It will be apparent from this synopsis that a not inconsiderable proportion of the cases present features that invalidate a diagnosis of classical pernicious anaemia, whilst in others the available evidence does not necessarily render this diagnosis proven. Nevertheless, it may safely be accepted that in a number of the cases the anaemia was hyperchromic and macrocytic, responded to liver therapy, and was therefore presumably megaloblastic.

## Case reports

**Methods.** In each of the cases to be reported the examination of the peripheral blood followed conventional lines. The haemoglobin determinations were by the Haldane method (100 per cent. = 13·8 gm. Hb.). Price-Jones' curves were not constructed, the extent of macrocytosis being assessed by careful inspection. Sternal marrow films were made by the squash method (Davidson, Davis and Innes, 1943) and stained by the May-Grünwald technique.

The liver extracts used in the treatment of the patients were from batches of known potency in cases of Addisonian pernicious anaemia. The proteolysed liver administered orally in cases 2 and 3 was the whole liver preparation described in a previous publication (Davis et al. 1943).

**Case 1.** D. M., a girl aged thirteen years, was first admitted to hospital on May 27, 1941, with a complaint of weakness, diarrhoea and pains in the limbs of a month's duration.

Interrogation of her mother, who was an intelligent woman of the superior working class, elicited the information that the child had been small and immature for her age, but she had always been active and apparently healthy until a few months previously when gradually increasing pallor was first noticed. No history could be obtained of any previous alimentary abnormalities. The child's appetite seemed always to have been good, and the diet satisfactory. She had never previously suffered from vomiting or diarrhoea. The passage of abnormal stools had never been noted.

PHYSICAL EXAMINATION revealed a pale undernourished girl weighing only 56 lb. No enlargement of the spleen, liver and lymph glands was detected. The skin was dry and scaly but the tongue moist and clean with a normal surface. No signs of jaundice or purpura were seen.

LABORATORY INVESTIGATIONS. Gastric analysis showed no free acid in the resting juice, but 10 units of HCl were recorded after the injection of 0·5 mgm. histamine. The haemoglobin was 20 per cent.; red cell count, 860,000 per c.mm.; colour index, 1·16; reticulocytes, less than 1 per cent.; white cells, 1,400 per c.mm. The red cells displayed anisocytosis and macrocytosis. The white cells showed a granulopenia, no primitive cells being seen.

Sternal puncture revealed a megaloblastic marrow picture with a relative granulocyte maturation arrest at the myelocyte stage, the picture being similar to that seen in pernicious anaemia in the relapse phase (see fig. 1 and 2).

PROGRESS. Ferrous sulphate was given by mouth and injections of anahaemin 4 c.c. twice weekly. Four days after the first injection a reticulocyte count of 10 per cent. was recorded, and this was followed by a progressive rise in haemoglobin, red cells and white cells, the patient being discharged on July 9, 1941, six weeks after admission, with a blood count of: haemoglobin, 75 per cent.; red cells, 3,650,000 per c.mm.; colour index, 1·03, and white cells, 4,600 per c.mm. Her general condition was now much improved, and all symptoms had completely disappeared.

After the patient's discharge from hospital injections of anahaemin, 2 c.c., were continued fortnightly, but the blood condition showed no further improvement.

SECOND PERIOD IN HOSPITAL. She was readmitted to hospital on Jan. 3, 1942, with a haemoglobin reading of 65 per cent., red count of 2,650,000 per c.mm., and a colour index of 1·23. The mean cell volume determined on this occasion was 140 c.$\mu$. A sternal puncture was performed, and the marrow picture was again found to be megaloblastic. Free HCl was found in the resting gastric juice.

The stools were normal, no steatorrhoea or diarrhoea being noted. She remained in hospital on this occasion for only twelve days during which she received a total of 24 c.c. pernaemon with no reticulocyte response or significant improvement in the red cell count.

On her return home the patient received pernaemon 4 c.c. weekly and subsequently her blood

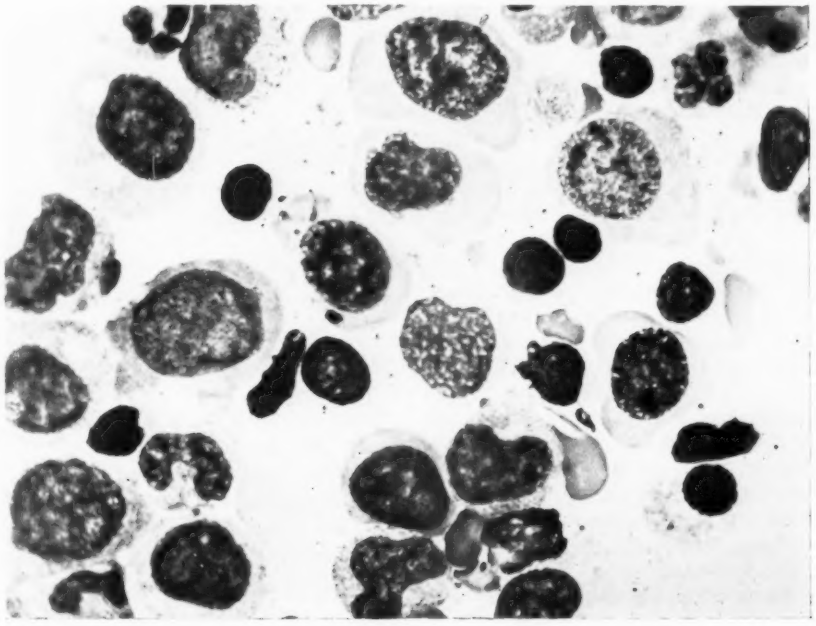

FIG. 1.—Microphotograph of sternal marrow film from case No. 1, showing megaloblastic erythropoiesis. ×800.

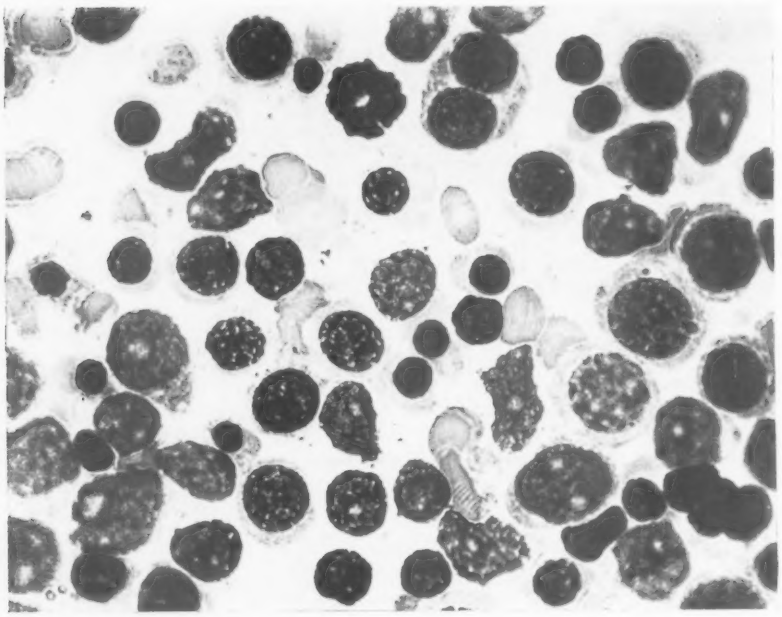

FIG. 2.—Microphotograph of sternal marrow film from a case of iron deficiency anaemia showing normoblastic erythropoiesis. Compare with figure 1. ×800.

picture showed a slow but progressive improvement. After a few months the treatment was changed to anahaemin 2 c.c. weekly supplemented with iron and ascorbic acid. On Oct. 25, 1943, the blood count was: haemoglobin, 94 per cent.; red cells, 4,620,000 per c.mm.; colour index, 1·02; mean cell volume, 92 c.$\mu$.; white cells, 5,200 per c.mm. The child appeared to be in good health but was still underweight. During the next few months, however, the patient complained of increasing fatigue on exertion and became paler, although she continued to receive anahaemin 2 c.c. weekly and ascorbic acid 150 mgm. daily.

THIRD PERIOD IN HOSPITAL. The patient was again admitted to hospital on March 3, 1944. She was now sixteen years of age, but her physical development was that of a girl several years younger. Her height was 57½ in. but her weight was only 72 lb. Secondary sexual characters were undeveloped, and menstruation had not started.

Several carious teeth were noted, and the tongue was smooth but not completely denuded. Apart from a few patches of impetigo on the face, the skin displayed no obvious abnormal features. The abdomen was somewhat full, but no enlargement of liver, spleen or other viscera was detected, nor were any lymph glands found to be enlarged. The bowel movements were normal, and it should be noted that at no time during the past two years had there been any symptoms of gastro-intestinal disorder.

Radiological investigation of the skeleton showed widespread decalcification and changes at the metaphyses similar to those seen in rickets. The sella turcica was normal in shape and size.

LABORATORY FINDINGS. Haemoglobin, 56 per cent.; red cells, 2,410,000 per c.mm.; colour index, 1.16; mean cell volume, 107·9 c.$\mu$.; reticulocytes, less than 1 per cent.; white cells, 5,600 per c.mm. The film showed a macrocytic blood picture.

Gastric analysis now revealed a histamine-fast achlorhydria. Stool analysis showed a total fat content of 26 per cent., of which 80 per cent. was split.

Serum calcium, 7·3 mgm. per cent.; plasma phosphorus, 4·6 mgm. per cent.; and plasma phosphatase, 95 units (modified Kay); icteric index, 4.

PROGRESS. One injection of anahaemin 4 c.c. resulted in a reticulocyte response of 5 per cent. and a subsequent rise in haemoglobin to 70 per cent., and of red cells to 3,480,000 per c.mm. at the end of a fortnight. Treatment was then continued with weekly injections of anahaemin and vitamin D, ascorbic acid, iron, calcium lactate, and ol. phosphorat. by mouth daily.

By April 26, 1944, nearly two months after re-admission to hospital, her weight had increased by 5 lb., and the haemoglobin had risen to 84 per cent. with 4,510,000 red cells per c.mm. On this day, however, she suffered a green-stick fracture of the left femur.

**Comment.** From the haematological aspect, the significant features of this case are the development of a severe megaloblastic anaemia at a time when free hydrochloric acid was present in the patient's gastric juice, and the tendency to relapse on maintenance treatment with high dosage of parenteral liver extracts. The response of the patient to this form of therapy is difficult to explain, particularly with regard to the months immediately preceding her last admission to hospital when her blood condition showed progressive deterioration. Further questioning of mother and doctor provided confirmation that at this time she received regular injections of anahaemin. There is no reason to doubt the potency of this material since it was from the same batches, and obtained from the same source as that supplied to the hospital. The prompt haematopoietic response to a single injection of 4 c.c. of anahaemin given immediately after her re-admission

to hospital is accordingly puzzling. The only factors of possible therapeutic significance that can be attributed to hospitalization were the rest in bed and possibly a more nutritious diet.

The defective haematopoiesis would appear to have its origin in some nutritional disorder rather than in inadequate production of intrinsic factor, for the delayed somatic development and the generalized skeletal de-calcification point to an abnormality in absorption or metabolism. The nature of such an abnormality is obscure however. In view of the child's appetite and dietetic history it would not appear to be attributable to an inadequate intake. The absence of history of vomiting, diarrhoea or steatorrhoea renders a retrospective diagnosis of coeliac disease questionable.

It is significant, however, that during the last admission to hospital a histamine-fast achlorhydria was demonstrable for the first time, for the development of achylia in a patient of this age is of course quite abnormal and indicative of a pathological condition of the alimentary tract. In view of this finding it may be argued that the case is one of Addisonian pernicious anaemia, but the fact that the achylia did not develop until two years after the onset of the severe megaloblastic anaemia, together with the other evidences of defective nutrition, makes such a diagnosis difficult to accept.

The possibility of a pituitary insufficiency was considered, since the association of this condition with achlorhydria and severe anaemia which may be macrocytic, has been described by Snapper, Groen, Hunter and Witts (1937). In the present case, although no definite evidence in support of such a conception has so far been provided, the possibility of endocrine dysfunction should obviously not lightly be discarded.

**Case 2.** J. B., a boy aged fourteen years, was admitted to hospital on May 7, 1942, complaining of slight diarrhoea of nine months' duration and a recent loss of one stone in weight. No evidence could be elicited suggestive of a defective diet or of any previous alimentary disorder. The previous personal and family medical history was not significant.

Examination revealed a pale, undernourished child with a red, smooth tongue, but no other abnormalities were detected. His height was 54 in. and weight 54 lb.

Examination of the blood showed a severe hypochromic microcytic anaemia, the count being: haemoglobin, 17 per cent.; red cells, 1,050,000 per c.mm.; colour index, 0·81; reticulocytes, 3 per cent.; white cells, 4,500 per c.mm.; platelets, 320,000 per c.mm. Red cell fragility was normal and no urobilinuria or other evidence of disordered bile pigment metabolism was noted.

Stool analysis showed 11·2 per cent. total fats, of which 55·8 per cent. were split. Radiological examination of chest and abdomen was negative. A tuberculin test gave a mild positive reaction.

PROGRESS. A blood transfusion was given and iron and ascorbic acid administered. Thereafter a rapid improvement in the patient's general and haematological condition occurred, but two weeks after admission to hospital a transient ascites appeared which lasted for ten days. After its disappearance a firm enlargement of the liver was noted, the lower edge of which extended 1 in. below the costal margin. This enlargement persisted. The patient was discharged from hospital with a red cell count of 5,290,000 per c.mm. with 96 per cent. haemoglobin in excellent health and weighing 74 lb. He remained well for some months, but then again began to lose weight and energy.

SECOND PERIOD IN HOSPITAL. He was re-admitted to hospital on May 25, 1943. Physical examination now showed a protuberant abdomen with the same degree of hepatic enlargement as previously noted. The spleen was not palpable, but apart from manifestations of anaemia no other clinical abnormalities were noted. His weight, however, was only 64 lb. with a height of 54½ inches.

LABORATORY FINDINGS. Blood examination now showed a macrocytic anaemia: haemoglobin, 44 per cent.; red cells, 1,800,000 per c.mm.; colour index, 1·22; reticulocytes, less than 1 per cent.; white cells, 3,300 per c.mm. The red cells displayed marked anisocytosis with many oval-shaped macrocytes, the picture being characteristic of pernicious anaemia. Sternal puncture revealed a typical megaloblastic picture. Icteric index, 13; blood cholesterol, 160 mgm. per cent.; Wassermann reaction, negative; gastric analysis, histamine-fast achlorhydria; stools contained no occult blood; fat analysis—total fats, 27 per cent. of which 33 per cent. were split.

PROGRESS. An injection of anahaemin 4 c.c. resulted in no haematopoietic response in ten days. Proteolysed liver was then given orally, ½ oz. daily; no iron or other haematinics being administered. This was followed by a reticulocyte response of 9 per cent. on the tenth day and a rapid and progressive rise in the red cell and white cell counts. Reticulocyte counts were unfortunately not recorded throughout the first ten days of the proteolysed liver therapy, consequently it is probable that the maximum reticulocyte rise was higher than the figure noted above. The patient was discharged on July 17, 1943, with a red cell count of 4,500,000 per c.mm.; haemoglobin, 84 per cent.; colour index, 0·93; white cells, 5,400 per c.mm. and a gain in weight of 9 lb.

Subsequent to the patient's discharge from hospital the oral liver therapy was replaced by parenteral injections of a crude liver extract (plexan) 2 c.c. twice monthly. When seen five months later he was in excellent condition and the blood count was within normal limits, but the liver was still enlarged. On March 8, 1944, however, eight months after leaving hospital, the patient still felt quite well, but his blood condition had deteriorated to: haemoglobin, 80 per cent.; red cells, 3,820,000 per c.mm. Further injections of liver extract were now stopped and replaced by proteolysed liver, ¼ oz. daily given by mouth. A month later the haemoglobin had risen to 94 per cent. and the red count to 4,380,000 per c.mm. The white cell count was 8,600 per c.mm. The patient was in excellent health and there was now no evidence of hepatic enlargement. All treatment was now discontinued. Two months later, on June 14, 1944, the boy was still in excellent health, his haemoglobin being 90 per cent. with 4,440,000 red cells per c.mm. and white cells 5,400 per c.mm.

**Comment.** An interesting feature of this case is the onset of the severe hyperchromic macrocytic anaemia a year after the hypochromic microcytic anaemia.

Examples of anaemias changing from hypochromic to hyperchromic have been described in adults by Davidson and Fullerton (1938) and Miller and Dameshek (1941). The rarity of the phenomenon is emphasized by the first-mentioned authors who state that in a study of a thousand cases of hypochromic anaemia only three were known to develop a macrocytic anaemia subsequently.

Miller and Dameshek suggest that the transformation may result from a progressive disorder of the gastric mucosa leading first to achlorhydria and inadequate iron absorption and later to interference with production of intrinsic factor and consequent development of pernicious anaemia.

In the present case it is unfortunate that no gastric analysis was done during the stage of hypochromic anaemia, but it will have been noted that achylia was present after the onset of the hyperchromic stage. In spite of this it is thought that the under-developed physique of the boy which is highly suggestive of a generalized nutritional or metabolic abnormality, and the inadequate response to fractionated liver extracts, justify the rejection of a diagnosis of Addisonian pernicious anaemia.

As in the previous case, no definite etiological factor can be incriminated. In view of the development of ascites during the first admission to hospital, a diagnosis of abdominal tuberculosis was considered, since it was thought that a tuberculous involvement of the lacteals might have resulted in defective absorption and consequent anaemia. The subsequent course of the patient, however, provided no confirmatory evidence for such a diagnosis, although it does not necessarily warrant its final rejection.

The long-continued hepatic enlargement noted in this case makes it tempting to attempt to correlate this finding with the pathogenesis of the anaemia. It is conceivable that in the first place defective assimilation may have resulted not only in an iron deficiency leading to the hypochromic anaemia, but in a deficiency of methionine or other factors necessary for normal functioning of the liver, thus giving rise to disease of this organ. The persistence of such a pathological condition after the correction of the hypochromic anaemia by adequate iron therapy, provides a plausible explanation for the subsequent development of the macrocytic (megaloblastic) anaemia. The response of the macrocytic anaemia to proteolysed liver therapy and the eventual regression of the hepatomegaly may be explained not only by haematopoietic virtue of proteolysed liver, but by its high content of amino-acids including methionine (1 per cent.) which would presumably be of peculiar value in correcting a state of hepatic dysfunction. It will be appreciated that the foregoing suggestion is purely hypothetical, and furthermore does not attempt to explain the nature of the underlying faulty assimilation.

An observation of considerable therapeutic interest was the failure to maintain satisfactory haematopoiesis with injections of plexan, and the subsequent success of proteolysed liver orally after the patient's final discharge from hospital. Reference has already been made to data to be published elsewhere demonstrating the successful treatment with proteolysed liver of cases of megaloblastic anaemia shown to be refractory to treatment with anahaemin. The behaviour of the present case during the patient's second period in hospital provides further evidence on this point. Anahaemin, however, is a refined, and highly purified fractionated liver extract, whereas plexan is stated to be a crude extract containing factors of possible haematinic value not present in the more highly refined extracts. So far as I am aware no trial has previously been reported in which the comparative merits of such a crude liver extract and of proteolysed liver have been assessed in the treatment of a refractory anaemia.

**Case 3.** This case has been included by Davis and Davidson (1944) along with other examples of megaloblastic anaemias refractory to treatment with parenteral liver extracts but responsive to proteolysed liver therapy. As an example of megaloblastic anaemia in childhood, however, it is considered that a brief account of the case merits inclusion in the present paper.

The patient, J. R., was a girl aged twelve years admitted to hospital on August 12, 1943, on account of progressive loss of weight and energy and of increasing pallor. These symptoms had been noticed only during the preceding two months. Formerly, she had always been a healthy, energetic child, and there was no history suggestive of coeliac disease or other alimentary disorder. Her social circumstances were comfortable and provided no grounds for suspecting inadequacy of diet.

On examination the girl was found to be very pale and listless. Her weight was 70 lb. No signs of purpura or of jaundice were evident, although the gums were spongy and bled easily. The tongue was clean, moist and not smooth. The liver was firm, and its lower edge was palpable one inch below the costal margin. No enlargement of the spleen or lymph glands was detected, nor were any other clinical abnormalities noted. The stools appeared to be normal, and there was no diarrhoea. Radiological examination of the chest was negative, but confirmed the hepatic enlargement.

LABORATORY FINDINGS. Examination of the blood revealed a macrocytic anaemia with pronounced anisocytosis and poikilocytosis with numerous large macrocytes. The red cell count was 1,130,000 per c.mm.; haemoglobin, 32 per cent.; colour index, 1·42; reticulocytes less than 1 per cent.; white cells, 4,600 per c.mm. Platelets were not counted, but were scanty in cover-slip films. Sternal puncture showed a typical megaloblastic marrow picture. The Wassermann reaction was negative. The gastric juice contained free hydrochloric acid. The icteric index was 13; no excess of urobilinogen was present in the urine. The stools were repeatedly examined for occult blood with negative results, and a fat analysis showed 13·5 per cent. total fat of which 71·4 per cent. was split.

PROGRESS. An injection of anahaemin, 4 c.c.,

was given and repeated after six days with no evidence of any haematopoietic response. Five days after the second injection the haemoglobin fell to 30 per cent. and the patient developed a retinal haemorrhage. A blood transfusion of one pint was given which raised the haemoglobin to 44 per cent. and was followed by two more injections of anahaemin (4 c.c.) without response; the haemoglobin falling to 32 per cent. four days after the last injection.

The patient was then put on proteolysed liver by mouth, working up to 1½ oz. daily. This was followed by a reticulocyte count of 28 per cent. on the fifth day after the start of this form of therapy and a progressive clinical and haematological improvement. On Sept. 28, 1943, twenty-seven days after beginning the proteolysed liver, the red cell count was 4,500,000 per c.mm.; the haemoglobin 85 per cent.; colour index, 0·94 and the white cell count 6,000 per c.mm. The patient's general condition was now considerably improved and she had gained 10 lb. in weight since admission to hospital. She was accordingly discharged home and did not receive any further liver or any other haematinic treatment.

When seen on Oct. 26, 1943, she was feeling very well and her blood picture was normal, the red cell count being 4,500,000 per c.mm. with haemoglobin 90 per cent. The lower edge of the liver was just palpable and was neither firm nor tender. Two months later her haemoglobin was 100 per cent. with 4,900,000 red cells per c.mm. and her general health was excellent, and has remained so during recent months.

**Comment.** The presence of free hydrochloric acid in the gastric juice; the failure of response to injections of liver extract, the recovery on proteolysed liver and subsequent maintenance of health without further treatment are all considered to be features which invalidate a diagnosis of Addisonian pernicious anaemia.

No satisfactory explanation can be advanced for the apparently temporary failure in haematopoietic function displayed by this patient. The rapid loss of weight which accompanied the development of the symptoms of anaemia is suggestive of a temporary failure in absorption from the alimentary tract, but the absence of vomiting, diarrhoea or steatorrhoea renders this explanation purely conjectural. The slight degree of hepatic enlargement cannot with conviction be considered evidence of a primary disease of the liver, since such minor degrees of hepatomegaly are commonly found as secondary manifestations in many forms of anaemia, but on the other hand it is of course open to a hypothetical explanation similar to that considered in connexion with case 2.

In the meantime the child will need to be kept under observation since only time will tell whether the failure in haematopoiesis was a temporary incident or whether it was the prelude to a permanent disorder.

## Discussion

No further detailed discussion of the cases described in this paper is called for since their salient clinical and haematological features have already been considered. Certain generalizations may, however, be drawn from a consideration of the three cases in relation to the questions of diagnosis, pathogenesis and treatment.

Based solely on the haematological findings and the morphology of the sternal marrow films, a diagnosis of pernicious anaemia would have been warranted in all three cases, but in each case consideration of various clinical features renders such a diagnosis untenable or, at least, improbable. The pathogenesis in each case was obscure. In cases 1 and 2, circumstantial evidence points to long-standing nutritional dysfunction, but there is no adequate evidence for the diagnosis of any pathological or clinical entity of likely etiological significance. The etiology of the case 3 is still more obscure, since in this case, the failure in haematopoiesis seems to have been of a temporary nature.

The response to treatment was unusual in all cases. In case 1, maintenance of haematopoiesis at anything approaching an adequate level called for injections of liver extract in a dosage considerably exceeding that required in straightforward cases of pernicious anaemia. The other two cases were shown to be completely unresponsive to parenteral liver therapy but readily amenable to proteolysed liver given by mouth.

Reference has already been made to a communication to be published elsewhere (Davis and Davidson, 1944) dealing with the successful treatment with proteolysed liver of cases of megaloblastic anaemia which had proved refractory to injections of fractionated liver extracts. The significance of these observations is discussed in the paper referred to and will accordingly not be considered further here. It may be noted, however, that it is suggested that the arrested megaloblastic maturation in these refractory anaemias results from a deficiency of some additional haematopoietic factor, present in proteolysed liver but absent, or present only in inadequate quantity, in fractionated liver extracts. The possible effect of proteolysed liver therapy on hepatic dysfunction associated with anaemia has already been referred to in connexion with case 2.

## Summary and conclusions

1. The term megaloblastic anaemia is defined, and its pathogenesis is discussed.

2. Previous reports of macrocytic anaemias in childhood are reviewed, and attention is drawn to the rarity of the condition and to the inadequacy of the data for the justification of a diagnosis of Addisonian pernicious anaemia in most of the cases.

3. Three cases of megaloblastic anaemia are described in children aged twelve, thirteen and fifteen years. The pathogenesis of these cases is considered.

Although the blood and sternal marrow pictures were typical of pernicious anaemia, arguments are advanced against the acceptance of this diagnosis in the present cases, in all of which it is believed that defective assimilation from the alimentary tract may

have been an etiological factor of paramount importance.

Two of the cases proved refractory to parenteral injections of liver extracts of known potency but responded promptly to proteolysed liver administered orally.

In one case the macrocytic, hyperchromic anaemia was preceded a year earlier by a severe hypochromic anaemia.

**Acknowledgements**

Thanks are due to Professor L. S. P. Davidson for helpful advice and criticism, to Professors W. T. Ritchie, O.B.E., and D. M. Dunlop and to Dr. W. D. D. Small, C.B.E., for their kindness in granting facilities for studying patients under their care, and to Dr. D. Riding of Messrs. Evans, Lescher and Webb for supplies of proteolysed liver.

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# REFRACTORY ANAEMIA (FANCONI TYPE)

## ITS INCIDENCE IN THREE MEMBERS OF ONE FAMILY, WITH IN ONE CASE A RELATIONSHIP TO CHRONIC HAEMOLYTIC ANAEMIA WITH NOCTURNAL HAEMOGLOBINURIA (MARCHIAFAVA-MICHELI DISEASE OR 'NOCTURNAL HAEMOGLOBINURIA')

BY

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Orthochromic or hyperchromic anaemias, resistant to all forms of treatment, comprise a well-recognized, but probably heterogeneous, group of blood disorders for which the general term 'refractory anaemia' has been recently suggested (Bomford and Rhoads, 1941). Their origin is obscure, but the fact that similar syndromes may follow exposure to poisons such as certain aromatic hydrocarbons suggests that in some cases at least the formation of an endogenous haemotoxic metabolite may be a causal factor. That a constitutional element may sometimes be involved is shown by the rare occurrence of severe refractory anaemia in several members of the same family. Fanconi's description in 1927 of fatal anaemia in three brothers, all under seven years of age, appears to be the first recorded example of this association.

The present communication deals with the incidence of anaemia of this type in two brothers observed for a number of years. One patient (C. H.) has died and hypoplasia of the marrow was found at autopsy; the other (A. H.), who has now been ill for ten years, has made a partial recovery. A cousin (M. H.), a girl aged twelve years, has also died recently of 'aplastic anaemia' in another hospital. She was an only child and of similar genetic constitution to that of the other two patients, for her father and mother were brother and sister respectively of the parents of the two affected boys. The boys' three sisters and their parents appear to be healthy, and no other relative, save M. H., has suffered or has died from anaemia as far as could be ascertained. A further unusual feature has been that increased haemolysis has played a part in the development of the anaemias, at least in the case of A. H. In this instance an abnormality affecting the erythrocytes identical with that found in nocturnal haemoglobinuria has been repeatedly demonstrated.

### Clinical description

**1. C. H.** This boy was first under observation in March, 1933 when he was nine and three-quarter years of age. He was said to have been always pale, but definite anaemia dates from a severe epistaxis a month before admission. He did not properly recover from this and was kept in bed, becoming increasingly pale and listless. He had never been a robust child and had suffered from pneumonia on three occasions, winter bronchitis, measles, mumps and ringworm. He was the third of a family of five children. Physical examination showed a small, extremely pale child, 43½ lb. in weight. The only abnormal physical signs, excluding severe pallor, were haemic cardiac murmurs, scattered purpuric spots on arms and legs and slight oozing from the gums. The edge of the liver was just palpable but no enlargement of the spleen or of the superficial lymph nodes could be detected. There was an ill-defined mass in the abdomen to the left and below the umbilicus which was later found to be an enlarged and displaced left kidney.

Examination of the urine revealed no abnormality. Laboratory investigations showed a severe hyperchromic anaemia with leucopenia and thrombopenia. An average of six blood counts, done before transfusion was resorted to, gave the following figures:—erythrocytes 1,290,000 per c.mm., haemoglobin (Haldane) 30 per cent., colour index 1·15; leucocytes 1,800 per c.mm., neutrophil polymorphonuclears 35 per cent., lymphocytes 59 per cent., monocytes 2 per cent., eosinophils 3 per cent., myelocytes less than 1 per cent. There was slight anisocytosis and poikilocytosis, and occasional normoblasts were seen; reticulocytes averaged 1·8 per cent.; platelets 22,000 per c.mm.; bilirubin 0·1 mgm. per 100 c.c. plasma. Treatment with iron, copper, liver and adrenalin by injection proved ineffective, and he was later twice transfused. Clinically he was much improved by this and the haemoglobin level was raised to 68 per cent. The improvement in his blood was maintained without further transfusion for a period of three months until his discharge from hospital on July 25 (fig. 1). There was some improvement in the total leucocyte count; a maximum of 3,800 per c.mm. of which 43 per cent. were neutrophil polymorphonuclears being reached on June 19. The platelets remained low at 35,000 per c.mm.

He was re-admitted into hospital on November 6. He was transfused twice and discharged once more from hospital on January 21, 1934 with 98 per cent. haemoglobin. He was re-admitted on April 19, having been comparatively well in the meantime. His haemoglobin had by then dropped to 62 per cent. This was raised by transfusion to

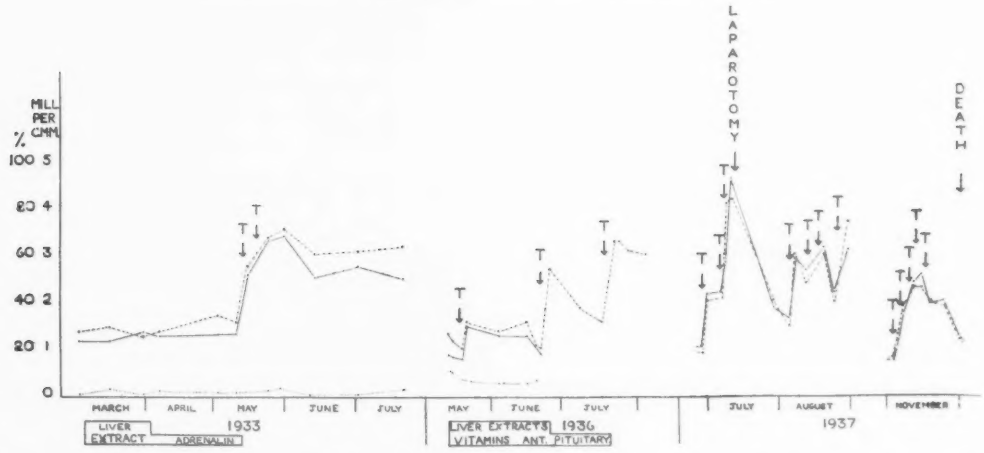


FIG.1.—Erythrocyte counts and haemoglobin and reticulocyte percentages during the first admission of C. H. into hospital, the early part of his second admission and the last two admissions. Erythrocyte counts are linked by continuous lines, haemoglobin percentages by interrupted lines and reticulocyte percentages by dotted lines. Transfusions are denoted by the letter T.

90 per cent. and he was discharged on April 29, then weighing 53 lb.

He was not seen again until May 8, 1936, two years later. He had kept fairly well during the intervening period, but in the month or so prior to re-admission he had become weaker. A remarkable feature was that he had hardly grown at all during the preceding two years; he weighed 51 lb., a little less than his weight in April 1934, and he was but one inch taller in height. A blood count showed a recurrence of severe anaemia; erythrocytes 870,000 per c.mm., haemoglobin 26 per cent., colour index 1·49, cell volume 10·2 per cent., mean. corp. vol. 118 cu.$\mu$; leucocytes 1,600 per c.mm. The percentage of reticulocytes was higher than before; 7·7 per cent. was the average of three observations. Physical examination revealed nothing more except that pallor was now combined with a slight generalized brownish colouration of the skin and this was particularly noticeable around the eyes. Several teeth were carious and his gums were oozing. He was kept under observation in hospital for eight months and was given numerous injections of liver extract (pernaemon forte) and preparations of vitamin A, C and D and anterior pituitary extracts, all without any beneficial effect. He received during this time seven transfusions of between 300 and 550 c.c. of fresh citrated blood. Examination of a gastric residue showed hypochlorhydria, but there was a good secretion of free HCl after the injection of 0·25 mgm. of histamine. An x-ray of the skeleton showed no abnormality except slight coarsening of the trabeculation and decalcification at the ends of the long bones. A barium meal revealed no abnormality in the upper gastro-intestinal tract. A sternum puncture showed a moderately active marrow with a leucocyte-nucleated erythrocyte ratio of 3:7 to 1:0.* He was discharged from hospital on January 17, 1937, but was re-admitted on May 19 severely anaemic with 13 per cent. haemoglobin. He was given two transfusions and was discharged a week later, only to be re-admitted on June 28 again critically ill. It was decided to perform a laparotomy to discover the nature of the puzzling abdominal tumour which had been felt on each admission. At operation the mass was found to be an enlarged kidney low in position and extending across the midline. No other abnormality was found and the spleen which appeared small was not removed. He stood the operation well but subsequently developed an irregular pyrexia ranging between 99° F. to 101° F., which persisted for the six weeks that he was kept under observation. He received three transfusions before the operation and four afterwards, but it was disturbing to notice that the beneficial effects of transfusion were becoming more transitory. A 20 per cent. fall in haemoglobin within four days was noticed on one occasion and a fall of 12 per cent. in the same period after a second transfusion. It seemed probable that erythrocyte formation was becoming increasingly difficult or that blood destruction at an increased rate was taking place. No decisive information was, however, available. He was discharged on August 29.

He was re-admitted for the last time on November 3, 1937, aged fourteen years and weighing 56 lb. He received five transfusions within a fortnight amounting in all to 1,600 c.c. of fresh citrated blood, and the haemoglobin was in this way raised from 15 to 46 per cent. His gums were bleeding on admission and a fortnight later swelling and oedema of the right cheek developed, associated with a sloughing area inside the mouth. The area of necrosis gradually spread until it had involved the palate and tonsillar fossae. His temperature had been gradually rising since admission and for the last fortnight fluctuated between 103° F. and 104° F. He died on December 2. An autopsy was performed ten hours after death.

**Post-mortem report**. The body was of a small pale boy in a moderate state of nutrition; the subcutaneous fat was limited in amount. There was a generalized dusky pigmentation of the skin particularly marked in the axillae, groins and inner aspect of the thighs. The outer side of the left cheek was discoloured and this corresponded to an area of necrosis within the mouth.

THORAX. The cardiac muscle was soft and pale;

* A differential count gave the following results:—leucocytes: neutrophil polymorphonuclears 4·8 per cent., metamyelocytes (band forms) 4·8 per cent., metamyelocytes (young forms) 42·8 per cent., myelocytes 21·6 per cent., myeloblasts 2·4 per cent., eosinophils 2·0 per cent., monocytes 2·0 per cent., lymphocytes 31·2 per cent. and plasma cells 3·2 per cent.; nucleated erythrocytes; haemocytoblasts 2 per cent., primary erythroblasts 43 per cent., normoblasts 55 per cent. The majority of the primary erythroblasts were late types. No megaloblasts were seen.

there were numerous sub-epicardial haemorrhages and ' tabby-cat ' striation beneath the endocardium. The cardiac valves and great vessels were normal. There was an excess of pericardial fluid and haemorrhages beneath the parietal pericardium. The pleurae contained effusions ; the bases of the lungs were collapsed and there were many sub-pleural haemorrhages.

ABDOMEN. The gastro-intestinal tract was normal except that the organs were pale : the mesenteric and para-aortic glands were hyperplastic. The liver was soft and appeared fatty and was a rich golden brown in colour. The spleen, which weighed 65 gm., appeared normal in colour and structure ; within its substance was a cavernous haemangioma, 15 mm. in diameter.

The pancreas, suprarenals, thyroid, thymus, pituitary and testicles were pale but showed no other macroscopic changes.

The kidneys were represented by a single horse-shoe-shaped organ weighing 220 gm. ; this was situated on the brim of the true pelvis below the bifurcation of the aorta. The right renal artery was derived from the right common iliac vessel and the left renal artery from the anterior surface of the aorta just above the point of bifurcation. A right and left ureter ran from the anterior surface of the kidney. The kidney substance was pale and soft and macroscopically normal.

BONE MARROW was examined from the sternum, skull, lumbar vertebrae and from the right femur. The marrow from the flat bones was pale red and semi-fluid in consistency ; it floated on water. That from the upper third of the femur was deeper red ; in the middle third there was an admixture of red marrow with fat, and marrow from the lower third appeared to be entirely fatty.

**Histopathology**

LIVER. There was a generalized fatty change of moderate degree with congestion and early necrosis of the parenchyma cells at the centre of the lobules. Much iron-containing pigment was distributed in the form of small granules within the liver cells and in Küpffer cells.

KIDNEY. There was no significant deviation from the normal except a moderate degree of granular degeneration and a small amount of fat within the cells of the convoluted tubules. No iron-containing pigment was identified.

SPLEEN. The spleen pulp was cellular and contained a moderate amount of blood. The Malpighian bodies were small. There was a generalized hyperplasia of the reticulum cells of the pulp and of the littoral cells of the venous sinuses, and many lymphocytes and plasma cells and occasional eosinophils and polymorphs were scattered throughout. A great deal of iron-containing pigment was present completely filling the cytoplasm of many reticulum cells. A few erythroblasts and normoblasts could be identified.

The section of the haemangioma showed it to be of the cavernous type with large endothelial lined spaces separated by thin connective tissue septa.

MYOCARDIUM. No significant changes except a slight degree of fragmentation of the muscle fibres.

LUNGS. Generalized oedema and small areas of haemorrhage were present ; the latter generally in the vicinity of bronchioles and surrounding large groups of organisms. There was some accumulation of mononuclear cells around the foci of infection, but few polymorphs.

PANCREAS, THYROID AND PITUITARY. No significant abnormalities.

TESTIS. The spermatic tubules were well developed but spermatogenesis was incomplete.

THYMUS. Sections showed a considerable degree of atrophy. The surviving tissue had been divided into small strips by strands of fat and collagenous tissue. Hassall's corpuscles were inconspicuous.

BONE MARROW. Marrow free from bony spicules was obtained from the centre of the shaft of the femur. Sections showed many fat cells with scattered haemopoietic cells lying between. The cells identified included late primary erythroblasts and normoblasts, and lymphocytes and plasma cells ; smaller numbers of myelocytes and eosinophils were present, but haemocytoblasts and adult polymorphs appeared to be absent. Much iron-containing pigment could be seen within phagocytic cells.

**2. A. H.** This boy aged twelve years, elder brother of C. H., was admitted into King's College Hospital on January 12, 1933. He had become increasingly pale and breathless for the previous three months and was said to have had a similar attack during the preceding summer from which he recovered. He had had no illnesses except chicken-pox, measles, mumps and whooping cough. Physical examination showed an intelligent and extremely pale boy. The lower edge of the liver was just palpable but the spleen could not be felt. There was no detectable enlargement of the superficial lymph nodes and no purpura of skin or mucosae. He weighed 80 lb. Blood counts on admission showed a profound anaemia, leucopenia and thrombopenia. The following figures are averages of fourteen counts made within a period of six weeks before he was transfused. Erythrocytes 860,000 per c.mm., haemoglobin 18 per cent., colour index 1·05 : leucocytes 1,600 per c.mm. ; polymorphonuclears 35 per cent., lymphocytes 60 per cent., monocytes 2 per cent., and eosinophils 3 per cent.; a very few myelocytes, myeloblasts and normoblasts were seen. There was a small amount of anisocytosis and polychromasia, but little poikilocytosis. There was an average of 4·7 per cent. reticulocytes. Single observations showed that not more than 10,000 platelets per c.mm. were present, and that there was 0·1 mgm. bilirubin per 100 c.c. plasma. Examination of the gastric residue showed slight hypochlorhydria with a good response to histamine. The Wassermann reaction was negative. During this time he was treated intensively with liver by injection and later with ventriculin by mouth, but without benefit (fig. 2).

He was then given within three weeks a series of five transfusions totalling in all 1,850 c.c. of citrated blood and greatly benefited thereby. His haemoglobin was raised to 70 per cent. and only gradually fell to 48 per cent. ten weeks after the last transfusion. He was given three more transfusions and discharged from hospital on July 2 with 81 per cent. haemoglobin. He was seen several times during the next five months and re-admitted into hospital on January 15, 1934 for observation. His haemoglobin, which had fallen to 61 per cent. by September 5, 1933, had risen spontaneously and was now 82

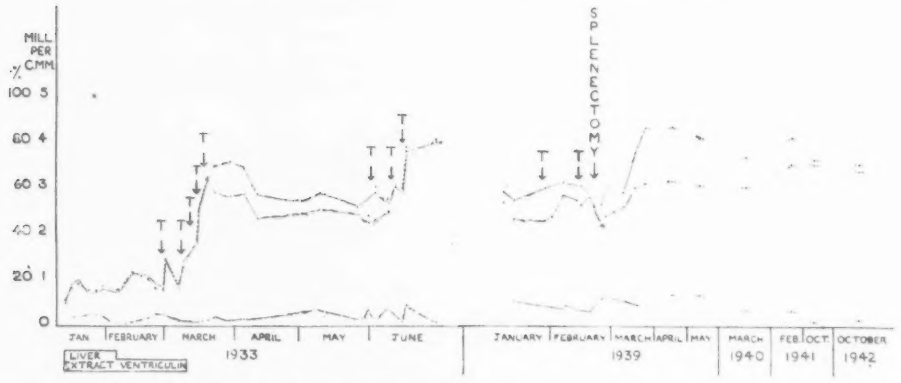


FIG. 2.—Erythrocyte counts and haemoglobin and reticulocyte percentages during the first and last admissions of A. H. into hospital. Erythrocyte counts are linked by continuous lines, haemoglobin percentages by interrupted lines and reticulocyte percentages by dotted lines. Transfusions are denoted by the letter T.

per cent. The leucocyte count had improved also ; there were 5,000 per c.mm., of which 50 per cent. were polymorphonuclears. Reticulocytes were then 7 per cent. and bilirubin 0·6 mgm. per 100 c.c. He was transfused and left hospital on March 4, with a haemoglobin of 88 per cent.

More than two years passed before he was seen again. During this period he had kept well and had not been transfused. Examination of his blood (May 1936) showed a mild degree of anaemia; erythrocytes 3,310,000 per c.mm., haemoglobin 68 per cent. with colour index 1·03 ; reticulocytes 6 per cent. ; cell volume 30 per cent., m.c.v. 91 cu.$\mu$, platelets 175,000 per c.mm. ; bilirubin 0·3 mgm. per 100 c.c. His blood was again examined in January 1937 and the haemoglobin was found to be 50 per cent. On this occasion he was admitted into hospital with a history of epigastric pain and vomiting of two days' duration. The attack passed off within twenty-four hours and did not recur.

He was not seen again until January 6, 1939, when he was readmitted with a recurrence of severe epigastric pain. The pain was of a continuous nature and was located in the left epigastric region. It was severe enough to prevent sleep and was similar to that experienced three times before in the previous seven weeks. Each attack was accompanied by vomiting and disappeared spontaneously in twenty-four to forty-eight hours. His blood picture had somewhat altered. The colour index was now less than one, and there was considerable anisocytosis, poikilocytosis and polychromasia. Quantitative estimations gave the following figures: erythrocytes 2,760,000 per c.mm., haemoglobin 47 per cent., colour index 0·86 ; cell volume 22 per cent., m.c.v. 81 cu.$\mu$ ; reticulocytes 8·5 per cent. (average of four observations) ; leucocytes 2,100 per c.mm. ; erythrocyte fragility to hypotonic saline, normal ; bilirubin 0·3 mgm. per 100 c.c. A sternum puncture showed erythroblastic hyperplasia.*

A transfusion given on January 23 produced a severe febrile reaction lasting for thirty-six hours and no appreciable rise in haemoglobin, and when a further transfusion of 500 c.c. of fresh citrated blood was given a fortnight later a rise in temperature to 103·8° F. was associated with clinical jaundice the following day. Although there was no haemoglobinuria, a fall in haemoglobin of 2 per cent. indicated that a haemolytic episode had occurred. The patient was group A and had received group A blood ; the latter had appeared to be perfectly compatible to the direct matching test, and the fact that he had been subsequently shown to be Rh+ * makes it unlikely that the post-transfusion haemolysis was due to iso-immunization conditioned by previous transfusions. Laboratory tests have indeed provided another and quite unexpected explanation, for it has been established that A. H.'s erythrocytes behave in vitro in a similar manner to those of patients with nocturnal haemoglobinuria, a disease in which haemolytic reactions following transfusion are frequently encountered (see Dacie and Firth, 1943). A summary of the laboratory findings on this point is recorded in a later section.

Whilst in hospital A. H. experienced another severe attack of epigastric pain and this was followed by the passage of a small amount of blood in the faeces. The possibility of a recurring strangulation of the small intestine or of an intussusception was considered and a laparotomy was decided upon. This was performed on February 24, 1939 by Mr. H. C. Edwards, but no abnormality of the intestinal tract was discovered. The spleen was, however, enlarged and was for this reason removed along with two spleniculi, one as large as a grape and the other much smaller.

He made a good recovery from the operation and his haemoglobin rose from 44 per cent. on February 27 to 62 per cent. on March 18 when he left hospital. He was seen one month and two months later and reported that he felt well and was going to start work. His blood count appeared unaltered.

He has been seen four times since 1939 ; in March, 1940 there were 3,670,000 erythrocytes per c.mm., and the haemoglobin was 60 per cent. ; reticulocytes 7 per cent., leucocytes 8,800 per c.mm. and platelets 320,000 per c.mm. In February 1941 a small improvement was evident ; the haemoglobin was 70 per cent., but the reticulocyte count was unaltered. In October 1941, when next examined, a blood count showed no change except

* The nucleated erythrocyte-leucocyte ratio was 1:3 to 1:0. A differential count gave the following results :—leucocytes : adult polymorphs 0·5 per cent., metamyelocytes (band forms) 6·5 per cent., metamyelocytes (young forms) 41·5 per cent., myelocytes 17·5 per cent., myeloblasts 2·5 per cent., eosinophils 2·5 per cent., eosinophil myelocytes 4·0 per cent., monocytes 2·5 per cent., lymphocytes 21·5 per cent., and plasma cells 1·5 per cent. ; nucleated erythrocytes ; primary erythroblasts 74 per cent., normoblasts 26 per cent. The majority of the primary erythroblasts were medium to late forms. No megaloblasts were seen.

* Thanks are due to Dr. P. L. Mollison for performing this test.

that the reticulocyte percentage had fallen to 1·8 per cent. He was last seen in October 1942 having felt well enough in the previous year to work 60 hours a week as a mechanic. There was little change in his blood count; erythrocytes were 3,500,000 per c.mm. and haemoglobin 67 per cent., and reticulocytes 3 per cent. The erythrocyte fragility had been substantially reduced following the removal of the spleen and target cells were present in the peripheral circulation.

**Histopathology of spleen.** Weight, 350 gm. The cut surface of the spleen was brownish pink in colour with easily visible but small Malpighian bodies. The trabeculae and finer fibrous strands were moderately conspicuous ; there was no thickening of the capsule. In consistency, the spleen was firm and on section little blood escaped.

Sections showed that the spleen pulp was relatively abundant and cellular. The Malpighian bodies were normal in size and showed slightly increased activity of their germinal follicles. The pulp contained little blood ; its increased cellularity was due to a diffuse hyperplasia of reticulum cells causing partial obliteration of the pulp spaces. The venous sinuses were generally difficult to identify. Small numbers of fine collagen fibres were present within the pulp. There was no erythropoietic activity, but scattered lymphocytes and eosinophils could be seen throughout.

Iron-containing pigment was inconspicuous.

**The in vitro behaviour of A. H.'s erythrocytes. Laboratory findings demonstrating a relationship to nocturnal haemoglobinuria**

It had been observed early in January (1939) that a sterile sample of venous blood allowed to coagulate at 37° C. showed much lysis of the clot after twenty-four hours' incubation, but lack of time had delayed exploration of this phenomenon. A series of investigations undertaken after the haemolytic episode provoked by the transfusion has thrown some light on this mechanism. This appears to be identical with that operating in patients with nocturnal haemoglobinuria. In the course of nine series of observations made between February 1939 and October 1942 it has been demonstrated :—

(1) That haemolysis of venous blood allowed to clot undisturbed in small tubes starts after one hour and is well marked after two hours' incubation ; lysis is much slower at room temperature.

(2) That haemolysis of clotted blood could be largely prevented by aeration of the blood by gentle rotation in the tube before the onset of coagulation ; tests using washed patient's corpuscles and the patient's serum acidified with lactic acid or hydrochloric acid showed a sensitivity to H-ion concentration. Haemolysis was inhibited at pH 8 and was optimum at pH 7·0 to 7·4.

(3) That haemolysis, using the patient's corpuscles and serum, acidified to pH 7·2 was increased by the addition of fresh guinea-pig serum (complement) from which all anti-human heterolysin had been adsorbed ; no haemolysis was caused by guinea-pig serum in the absence of human serum.

(4) That the patient's corpuscles were haemolysed as readily in normal serum as in the patient's own serum.

(5) That normal corpuscles were not haemolysed by the patient's serum.

(6) That the patient's corpuscles were more sensitive than normal cells to the isohaemolysin and to an anti-human haemolytic serum prepared from a rabbit ; they were somewhat less sensitive than the corpuscles of a typical case of nocturnal haemoglobinuria investigated at the same time.

The amount of lysis of the patient's corpuscles produced by incubation in his own acidified serum has progressively decreased, and when last tested (October 1942) this was much less easy to demonstrate than in two typical examples of nocturnal haemoglobinuria investigated during the same period. When the abnormality was first discovered in 1939 incubation for one hour caused as much as 25 per cent. haemolysis of a 1 per cent. suspension of patient's cells in acidified serum (1 in 2). When the test was last repeated in October 1942 under the same conditions there was only 5 per cent. lysis. It is interesting to note that the reticulocyte count has fallen from between 9 to 13 per cent. in 1939 to 1·8 to 3 per cent. in 1941–42 suggesting a reduced rate of haemolysis latterly.

**Discussion**

The original laboratory findings of severe megalocytic hyperchromic anaemia with little anisocytosis poikilocytosis and polychromasia, the leucopenia with a relative lymphocytosis, the thrombopenia, the presence of only a slightly reduced gastric secretion, the absence of hyperbilirubinaemia or of a significant number of abnormal cells in the blood supported the clinical diagnosis of ' aplastic anaemia ' in the case of both C. H. and A. H. The lack of response to treatment with liver by injection or to oral administration of hog stomach extract, iron and concentrated vitamin preparations provided additional support for this diagnosis and transfusion was resorted to as the only possible palliative measure.

In C. H. the relatively low reticulocyte count (average 1·8 per cent.) when he was first under observation was quite compatible with an anaemia of aplastic type : the small numbers present being thought to reflect the erythropoietic activity of small surviving foci of active marrow. When re-admitted in June 1936 significantly higher percentages of reticulocytes were observed (5·8 to 11 per cent.) and it seems likely that a measure of increased haemolysis was occurring despite the fact that no increase in plasma bilirubin was demonstrated. It is unfortunate that no in vitro tests for abnormal autohaemolysis were undertaken and also that no figures for urobilinogen excretion are available. The marrow puncture made in October 1936 which showed moderate erythroblastic activity does not provide decisive evidence. Therefore, although there is a possibility that increased blood destruction was a factor in the genesis of C. H.'s anaemia, positive evidence for this is lacking. On the other hand, the finding of hypoplastic marrow post-mortem shows that the original conception of C. H.'s anaemia as ' aplastic ' was correct, at least in part.

In the case of A. H., the data are more complete ; although no figures for pigment excretion are available, the observation of rapid in vitro autohaemolysis makes it highly probable that there was

increased blood destruction in vivo. It is not known if this was a factor from the first. Although A. H.'s reticulocytes were always increased in number, averaging 4·7 per cent. at his first admission, the profound anaemia, neutropenia and thrombopenia found at that time suggest that an 'aplastic' element was dominant. Again, the favourable effect of transfusions experienced in all his admissions except the last, shows that the haemolytic element was not pronounced at first; four reticulocyte counts as high as 7 per cent. and one of 9 per cent. made in 1933–34 suggest, nevertheless, that some measure of increased haemolysis was occurring. This was never sufficiently rapid to cause jaundice except as a result of the haemolytic crisis provoked by the last transfusion (February 1939). Haemoglobinuria was never present and haemosiderin was not found in the urine deposit.

It is difficult to know what effect splenectomy has had upon the course of the disease; it seems that the 'aplastic' element in his case was never as severe as in his brother even if the haemolytic element was more pronounced. Remissions occurred from the start, and the haemoglobin was not observed to fall below 46 per cent. between February 1934 and January 1939 despite the fact that he received no transfusions during this time. The final, and it is hoped permanent, remission, cannot, therefore, be attributed to removal of the spleen with any surety.

The clinical and pathological observations outlined above are remarkable on two counts: (1) the familial incidence, and (2) the haemolytic phase.

(1) **The familial incidence.** As has been mentioned in the introduction to this article a small number of cases of familial refractory anaemia in children associated with other constitutional abnormalities have been reported.

The three fatal cases described by Fanconi (1927) were boys aged, five, six and seven years. Severe hyperchromic anaemia; leucopenia with thrombopenia and a haemorrhagic diathesis were associated with microcephaly, hypoplasia of the testicles, convergent strabismus, increased tendon reflexes and a generalized brown melanin pigmentation of the skin. In 1938 Weil reported the incidence of refractory hyperchromic anaemia in two out of five children of one family. One boy aged seven years died after a nine months' illness during which haemorrhages were prominent. In addition to anaemia there was a well marked dusky pigmentation of the trunk, an inguinal hernia and an undescended testicle. The second boy was affected when nine years of age A dusky pigmentation of the skin was associated with obesity the onset of which coincided with the development of anaemia; the right testicle had not descended and that on the left side was small. His anaemia was hyperchromic and there was leucopenia, granulopenia and thrombopenia. He was never as severely ill as his brother and was kept under observation for four years, being treated by transfusions and thymic and testicular extracts. The last appeared to bring about the descent of the right testicle and this was associated with signs of puberty. Samples of marrow from the sternum were examined on three occasions; at the first puncture few marrow cells were obtained, but the later samples showed erythroblastic hyperplasia. When last seen four years after the onset of anaemia a blood count showed 3,070,000 erythrocytes per c.mm. with 65 per cent. haemoglobin; there were 2,200 leucocytes per c.mm. of which 10 per cent. were polymorphonuclears; reticulocytes were 1·2 per cent. and platelets 75,000 per c.mm. Weil also described a sporadic case which he believed to be of a similar type to the above. This patient was a girl aged six years who suffered from a severe hyperchromic anaemia, leucopenia and thrombopenia and died after an illness of eighteen months' duration. Her anaemia was associated with a brown pigmentation of the skin, particularly of the abdomen; a congenital bilateral anomaly of the thenar muscles preventing opposition was also present. Another example of a familial incidence has been reported by Hjorth (1940); he described a severe hyperchromic anaemia in a brother and sister both aged eight years at the time of onset The anaemia was associated with leucopenia, thrombopenia, and a haemorrhagic diathesis; in the boy there was hypoplasia of the marrow, thymus and testicles. There were also congenital bony deformities; clubfoot with an absent calcaneus and congenital luxation of the hip respectively. Similar deformities were present in two maternal cousins and a paternal cousin lacked both thumbs. There was a high incidence of abortion in this family affecting ten out of seventeen pregnancies; this was apparently not due to syphilis. Another instance of sporadic anaemia in a boy aged seven years, associated with abnormalities of development has been reported by Uehlinger (1929); in this case, anaemia, leucopenia and thrombopenia were accompanied by pigmentation of the skin, an absence of the left thumb and hypoplasia of the right one, and hypoplasia of the testicles. At autopsy a partially fatty marrow was observed and the right kidney and ureter found to be absent; the left kidney was enlarged with a double pelvis. A similar sporadic case has been recorded by van Leeuwen (1933). The patient was a boy who died after an illness of five years' duration, having then the appearance of an eight- to ten-year-old child, although fourteen years of age. Anaemia was severe and there was thrombopenia and slight leucopenia. Splenectomy was undertaken without benefit. A generalized dusky pigmentation of the skin was present, and his right thumb was deformed. Post-mortem showed, in addition to signs of severe anaemia, marked hypoplasia of the bone marrow, an absence of the right kidney, hypertrophy of the left kidney and ureter, an absence of the first right metacarpal and hypoplasia of testicles and thymus.

The reports of Fanconi, Weil, Hjorth, Uehlinger and van Leeuwen have many features in common; developmental abnormalities, particularly of the hands and kidneys, pigmentation of the skin and hypoplasia of the gonads were in each case associated with a hyperchromic anaemia, leucopenia and thrombopenia. It is likely that the present family belongs to the same group. A. H. is a well-developed young man and presents no unusual stigmata, but in C. H.'s case pigmentation of the skin, and a failure to grow were striking features. His kidneys were fused medially and low in position.

As far as adults are concerned Bomford and Rhoads (1941), who studied sixty-six patients, concluded that there was no evidence of a hereditary predisposition. Nevertheless, they reported that in two instances sisters of their own patients had died of anaemia of unknown nature, and in a further case a brother of the patient had died eighteen years before of benzol anaemia. It is interesting to note that there appeared to be a possible association between endocrine abnormalities and anaemia in certain patients out of the series of Bomford and Rhoads ; two patients were eunuchs, in two others hyperthyroidism was also present, and in four the onset was concurrent with the menopause. In several other patients pigmentation of the skin was conspicuous.

It is doubtful if there is any justification for making any absolute separation between the familial examples of refractory anaemia met with in children and the more frequent sporadic cases of childhood and adult life, at least until observations on pathogenesis demonstrate conclusive differences. It seems likely that neither developmental abnormalities, pigmentation of the skin nor endocrine abnormalities are specifically associated with the familial type, and it may be recalled that Weil, Uehlinger and van Leeuwen have observed cases of refractory anaemia in childhood associated with developmental abnormalities in which no familial incidence could be established. Moreover, it is possible that a hereditary tendency to refractory anaemia is more frequent than the report of Bomford and Rhoads would suggest.

Huber (1939) has recently investigated the blood pictures of members of three families in which 'panmyelophthisis' had occurred. In each case three generations were studied ; in his first family twenty-three relatives were investigated, and of these six members had less than 2,500 polymorphonuclears per c.mm., and in three of these there were more lymphocytes than polymorphonuclears. Out of fifteen members of the second family, three had less than 2,500 polymorphonuclears per c.mm. and one member (a male) a slight anaemia (erythrocytes 3,800,000 per c.mm., haemoglobin 75 per cent.). In his third family three out of eighteen members showed a neutropenia, 37 per cent. polymorphonuclears out of a total leucocyte count of 4,600 per c.mm. being the lowest value observed. Huber also investigated eleven relatives of a patient suffering from anaemia due to exposure to trichlorethylene ; none showed leucopenia.

These results are interesting and need confirmation. They emphasize the possible rôle of endogenous factors, in part inherited, in the genesis of refractory anaemia.

### 2. The haemolytic phase and the relationship to nocturnal haemoglobinuria

It has been only recently recognized that increased haemolysis may play a part in the genesis of a substantial proportion of refractory anaemias.

Rhoads (1939) records the results of a quantitative investigation of the excretion of urobilinogen by thirty such patients ; half of these showed a daily excretion greater than the normal of 150 mgm. even when no account was taken of the degree of anaemia (more accurately of the total mass of circulating haemoglobin) at the time. The average daily figure varied from 172 to 570 mgm., the mean of fifteen cases being 308 mgm. This increased breakdown of blood is not confined to those cases of obscure endogenous origin, but may also be observed in poisoning due to benzol and has been produced experimentally in a dog given large doses of oestradiol monobenzoate (Rhoads, 1939).

The part that increased haemolysis probably played in the production of the anaemia affecting the subjects of this report has already been discussed, and attention has been drawn to the ineffectiveness of transfusions given to C. H. during his last two admissions and to the haemolytic reaction ultimately provoked in A. H., which led to the demonstration of in vitro autohaemolysis of a type not previously recorded except in patients exhibiting the clinical picture of nocturnal haemoglobinuria. It is possible that this observation may not be as rare as it appears to be, for Rhoads referring to cases of refractory anaemia has recorded that transfusions . . . at certain stages seem to have been positively harmful, leading to acute haemolytic episodes, which suggests that a similar mechanism may have been operable.

The cause of increased haemolysis in refractory anaemia is not known. Except for mentioning that there seemed to be no correlation between the type of bone marrow and the presence or absence of signs of increased haemolysis, and that increased destruction within the marrow was considered possible, its mechanism is not discussed by either Rhoads and Barker (1938), Rhoads (1939) or Bomford and Rhoads (1941), who reported on the patients investigated in the Rockefeller Institute.

It is not suggested that the type of haemolytic mechanism demonstrated in A. H. is necessarily that operable in other examples of refractory anaemia in which there is increased blood destruction. Rather it is possible that refractory anaemia and nocturnal haemoglobinuria are disorders of parallel pathogenesis, perhaps both due to metabolic abnormalities, the one affecting erythropoiesis and the other disturbing factors, at present unknown, which may prevent or control the haemolysis of corpuscles in vivo. It may be that in the two patients we described both types of disorder were combined.

**Summary**

1. The incidence of refractory anaemia in three members of a family is described ; of the two boys personally investigated one, C. H., died after an illness of four years' duration and the other A. H., is alive after ten years' observation.

2. C. H. failed to grow during the last two years of his illness, and a dusky pigmentation of the skin developed. At autopsy his bone marrow was found to be hypoplastic : a developmental abnormality of the renal tract was also present, a single

horseshoe-shaped kidney being situated on the brim of the true pelvis.

3. A. H. has made a partial recovery. Investigation of a transfusion reaction led to the discovery of rapid autohaemolysis in vitro. Subsequent investigations showed that the mechanism of haemolysis was the same as in nocturnal haemoglobinuria.

4. The literature is reviewed and the few reports of familial refractory anaemia described. The similarity between the first patients and those investigated by Fanconi and later authors is stressed.

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# ERYTHROBLASTIC ANAEMIA WITH BONE CHANGES IN EGYPTIAN CHILDREN

## POSSIBLE COOLEY'S TYPE

BY

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Cooley's anaemia is a disturbance of the haemopoietic system characterized by a constant racial and familial incidence, a typical facial appearance, a progressive anaemia with large numbers of nucleated erythrocytes in the peripheral blood, enlargement of the spleen, distinctive changes in the bones and an invariably fatal termination. It was in 1925 that Cooley presented to the American Pediatric Society his first five cases. Later on, in 1927, he wrote his paper on: ' anaemia in children with splenomegaly and peculiar changes in the bones,' with a report of seven cases. In discussing the question of von Jaksch's anaemia, Cooley thought of giving this name to the disease he described, instead of coining a new name. But in 1928 he pointed out that this term was not suitable and he suggested the name ' erythroblastic anaemia ' because of the large number of nucleated erythrocytes in the blood. In fact the cases recorded originally by von Jaksch's differ in many respects from erythroblastic anaemia. In von Jaksch's cases large numbers of circulating nucleated erythrocytes were not a prominent or constant feature. The ultimate prognosis is good whereas erythroblastic anaemia is invariably fatal. No mention was made of any Mediterranean ancestry, characteristic facial or skeletal changes either in the original description of von Jaksch or in any subsequent accounts. It is possible, however, that many cases of erythroblastic anaemia had been labelled as von Jaksch's or splenic anaemia, and so lost for future reference.

Although most of the reported cases occurred in children of Mediterranean stock, Cooley and Lee (1932) believe that no great stress should be laid on the limitation of this or any other similar disease to a particular race. Cases have been reported in an English child by Bywaters (1938), in a Chinese girl by Foster (1940), and in a Hindu child by Mukherji (1938). Many cases had a history of brothers or sisters affected. Two cases in identical male twins have been recorded by Whipple and Bradford (1932) and in twin sisters by Baty, Blackfan, and Diamond (1932).

Certain clinical characteristics at once attract attention:

1. The face is mongoloid. This is partly due to a thickening of the malar bones and partly to a muddy yellowish discoloration of the skin.
2. The head is large and irregularly shaped with prominent frontal and parietal bosses.
3. The abdomen is prominent. This results chiefly from the increase in size of the spleen and liver.
4. The heart is enlarged in many instances, a point to which Nemet and Gross (1936) have drawn particular attention.

In most instances the skiagrams of the bones present a typical appearance. The long bones and small bones of the hands and feet are porous looking with sharp trabeculations and thinning of the cortex. When the process is more advanced and the cortex is exceedingly thin, pathological fractures may occur. Baty, Blackfan, and Diamond (1932) have reported pathological fractures in two cases. The cranial vault, in the early stages or in the mild cases, shows only thickening due to increased width of the diplöe and thinning of the outer and inner tables. In the advanced cases the profile view of the skull gives the appearance of a surface studded with small radiating spicules, which is sometimes likened to ' hair standing on end.' Somewhat similar changes have been reported in sickle-celled anaemia, in acholuric jaundice, and in erythroblastic anaemia associated with idiopathic steatorrhoea.

Examination of the blood reveals a severe hypochromic anaemia. The haemoglobin may be as low as 10 per cent. and the red cell count one million, or less. The red cells show a marked degree of hypochromia associated with an extreme variation in the size and shape of the cells. The predominating cell is very large with a markedly uneven distribution of haemoglobin. Cooley looks on these irregularly stained erythrocytes as characteristic of erythroblastic anaemia. The only other anaemia of childhood presenting a similar picture is sickle-cell anaemia. Erythroblasts and normoblasts in large numbers are present, but true megaloblasts are not found. Reticulocytes may number from 10 to as high as 30 per cent. There is usually a persistent leucocytosis of from 13,000 to 30,000 per c.mm. Caffey (1937) records the smallest number (4100) and

Whipple and Bradford (1932) the largest (116,000). Cooley believes the most striking feature is the frequent change from granulocytosis to lymphocytosis in the same case at short intervals.

The fragility of the red cells is not increased. On the other hand there may be an increased resistance of the red cells to hypotonic saline solutions. This serves to differentiate Cooley's anaemia from haemolytic (acholuric) jaundice in which the resistance is diminished.

The indirect van den Bergh reaction is positive, the icterus index is raised and the urobilinogen in the urine and stools is increased. The haemolysis, however, is not as marked as in congenital haemolytic jaundice or sickle-cell anaemia.

As regards etiology Cooley originally believed that the disease was haemolytic in nature and that the congenital characters placed it in the same class as acholuric jaundice and sickle-cell anaemia. Cooley and Lee do not now consider the disease as primarily haemolytic but rather that it is a dyshaemopoiesis due to a metabolic fault, congenital or racial, which also affects bone formation. The apparent relationship is nearer to pernicious anaemia, i.e. a defect of maturation exists and the immature cells which can be utilized only to a limited extent tend to accumulate at the site of production. If this thesis be correct Cooley's anaemia might be classified under the deficiency anaemias.

The bone marrow of these cases is said to be indistinguishable from that of pernicious anaemia, i.e. megaloblastic. Sternal marrow puncture performed on two of the author's cases revealed an erythroblastic reaction. Fawdry, of the Cyprus Medical Service, in a personal communication showed the author films of the sternal marrow of the twenty cases that he investigated in Cyprus and in all of them the reaction was erythroblastic.

The course of the disease is slow and progressively downhill. The shortest duration is seventeen months. The majority die before nine years, but some cases survive into adult life. Death usually results from infection.

Treatment is entirely symptomatic. Large doses of iron and liver proved useless. Splenectomy is not followed by improvement. A normoblastic crisis occurs after the operation. Wollstein and Kreidel (1930) described cases in which, after splenectomy the nucleated red cells numbered twenty times as many as before operation, and this state was still present four years after operation. Blood transfusion produces only a transient relief of symptoms. Nittis (1937) has lately reported good results with quinine therapy.

## Case reports

### First Case in a Greek Child

V. P., a female Greek, aged four and a half years, had been noticeably pale since two years, and two weeks before admission she had become progressively paler with bleeding from nose and had a mild pyrexia at the same time. The mother gave a history of two sons dying of severe anaemia at an early age. When examined it was obvious that the child was severely anaemic. The spleen and liver were definitely enlarged. There was oedema of feet and face. Examination of the blood revealed the following: Hb., 20 per cent.; red cells, 870,000 per c.mm. The red cells showed polychromasia ++, poikilocytosis +++ and anisocytosis +++. The erythrocytes showed the typically irregular distribution of the Hb. (fig. 1). Leucocytes 7800 per c.mm. Differential count: neutrophil segmented, 41 per cent.; lymphocytes, 48 per cent.; monocytes, 6 per cent.; neutrophil myelocytes, 4 per cent.; myeloblasts, 1 per cent.; normoblasts, 25 per cent., and erythroblasts, 9 per 100 leucocytes. Reticulocytes were 5 per cent. Fragility test was normal. Van den Bergh reaction showed a delayed direct result. The icterus index was 10 units. Radiographic examination of the bones presented a typical porous looking appearance of the long, small and flat bones, with sharp trabeculations and thinning of the cortex (fig. 2). The skull,

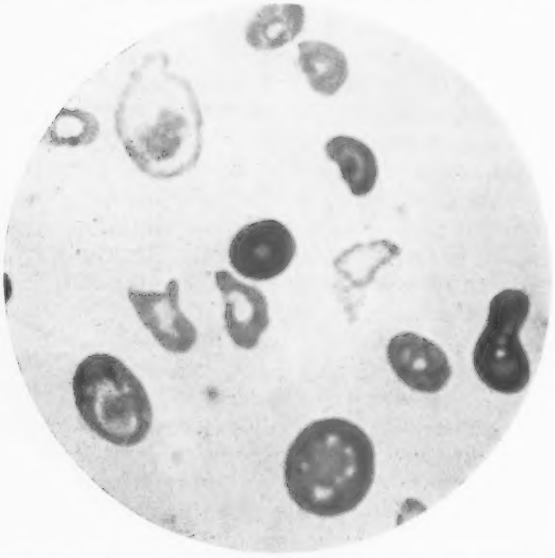

Fig. 1.—V. P. Blood film showing marked anisocytosis and poikilocytosis. Note the irregular distribution of Hb.

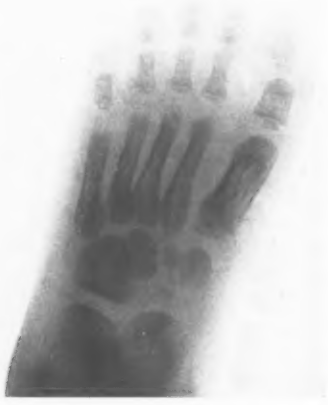

Fig. 2.—V. P. Skiagram of the bones of foot showing marked osteoporosis.

though showing medullary thickening and thinning of the tables, did not present the radiating spicules so characteristic of the advanced stage of the disease.

The child died at home two days after the examination and no autopsy was done. I had the opportunity of examining his brother and the blood picture revealed nothing of particular interest.

### Second Case in an Egyptian Child

M. M., a male, genuine Egyptian, aged ten years, admitted to the Children's Hospital for marked pallor. No family history of importance was obtained. Clinical examination revealed a mongoloid facies; severe pallor; marked enlargement of the spleen which reached as far down as the pelvis; liver was felt four fingers' breadth below the costal margin. Examination of the blood revealed the following: haemoglobin ranged between 20 and 25 per cent. throughout a period of six months in spite of massive doses of iron and liver extracts and repeated blood transfusions. Red cells numbered 2,000,000 per c.mm. The red cells showed marked anisocytosis, poikilocytosis, punctate basophilia and irregular distribution of the Hb. (fig. 3). Erythroblasts amounted to 25 and normoblasts to

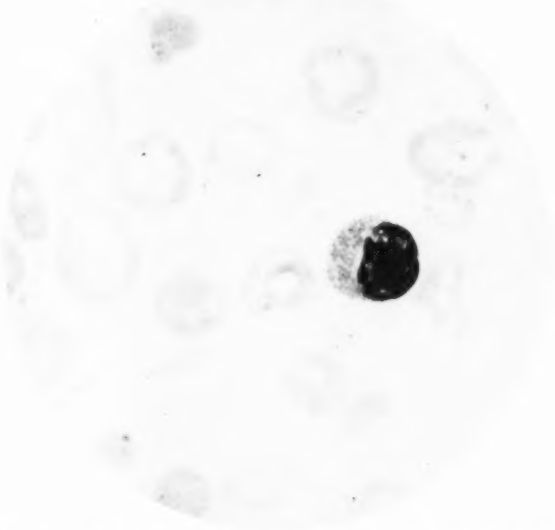

Fig. 3.—M. M. Blood film showing anisocytosis, poikilocytosis, irregular distribution of and Hb. erythroblastaemia.

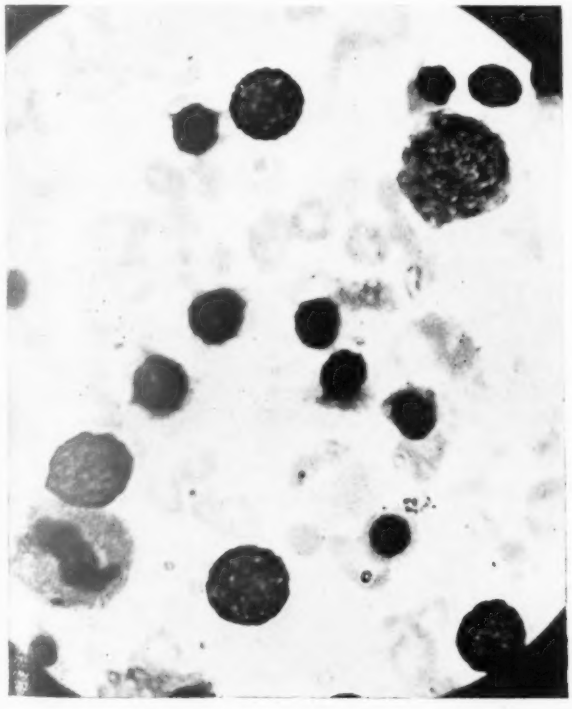

Fig. 4.—M. M. Bone marrow smear showing erythronormoblastic reaction.

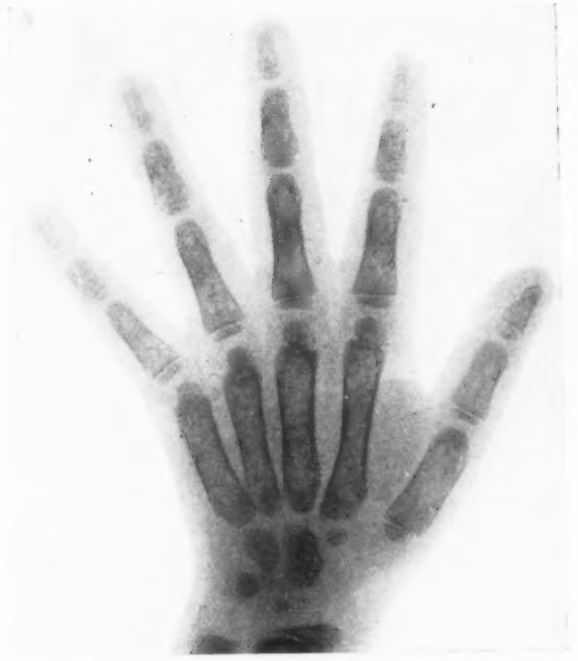

Fig. 5.—M. M. Skiagram of hand showing osteoporosis of small bones.

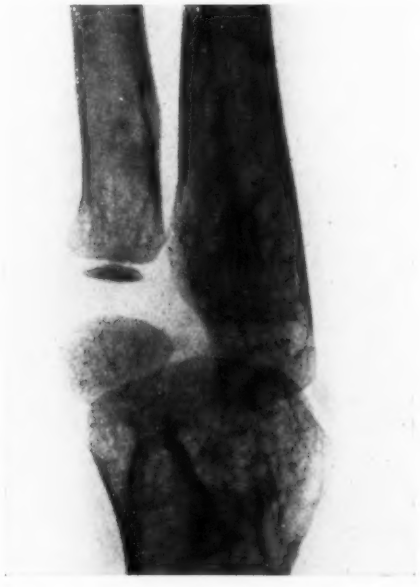

Fig. 6.—M. M. Skiagram of elbow showing osteoporosis at the ends of the bones.

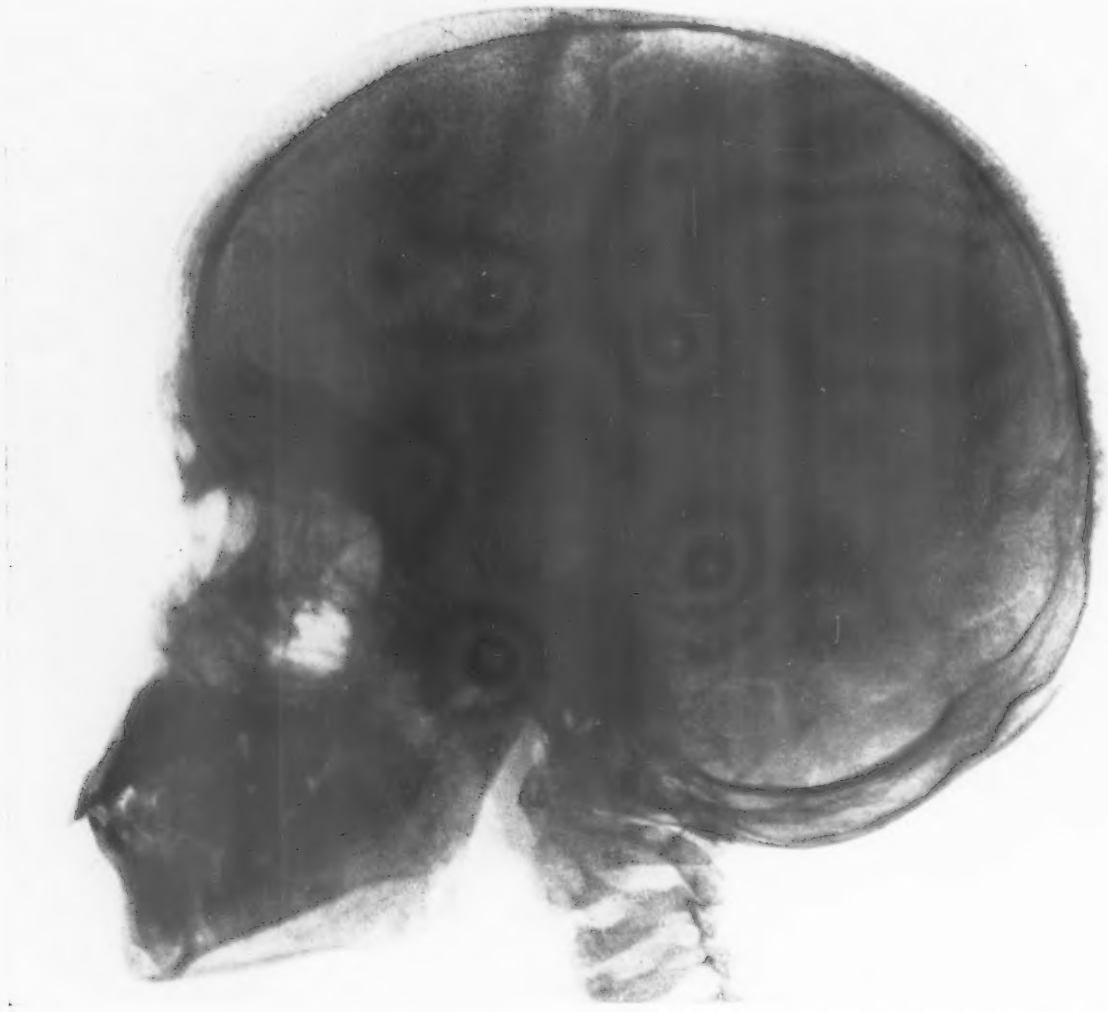

FIG. 7.—M. M. Skiagram of skull showing thickening of diplöe and thinning of inner and outer tables.

23 per 100 leucocytes. Leucocytes were 9600 per c.mm. Differential count: myeloblasts, 1 per cent.; premyelocytes, 4 per cent.; myelocytes, 12 per cent.; metamyelocytes, 10 per cent.; band forms (stab cells), 9 per cent.; mature polymorphs, 41 per cent.; eosinophils, 5 per cent.; monocytes, 2 per cent.; lymphocytes, 16 per cent.; reticulocytes were always below 5 per cent. Sternal marrow puncture revealed a marked erythroblastic hyperplasia (fig. 4). Van den Bergh gave a delayed direct reaction. The icterus index was 10 units and on one occasion rose to 50 units. Fragility test: red cells started haemolysis at a concentration of 0·25 (i.e. increased resistance). Blood films were repeatedly negative for malaria. Wassermann reaction negative. Stools repeatedly negative for parasites and ova. X-ray examination of bones revealed marked osteoporosis (fig. 5, 6); the skull showed thickening of the diplöe and thinning of the tables (fig. 7). X-ray examination of the heart showed marked dilatation, especially in the transverse diameter (fig. 8).

Nine months have passed since child was first seen. He is still alive and so far has failed to respond to haematinics and repeated transfusions.

### THIRD CASE IN AN EGYPTIAN CHILD

S. S., an Egyptian female, aged six years, was admitted for severe pallor and abdominal distension. Examination revealed a typical mongoloid facies, a markedly enlarged spleen reaching as low down as the pelvic brim and a moderately enlarged liver reaching four to five fingers' breadths below costal margin. Blood examination: Hb., 23 per cent.; red cells, 1,130,000 per c.mm.; leucocytes, 19,200 per c.mm.; myeloblasts, 0 per cent.; premyelocytes, 2 per cent.; myelocytes, 4 per cent.; metamyelocytes, 7 per cent.; staff, 10 per cent.; segmented, 35 per cent.; lymphocytes, 37 per cent.; monocytes, 1 per cent.; eosinophils, 4 per cent. There were 45 nucleated reds (practically all normoblasts) for each 100 leucocytes. Reticulocytes, 5 per cent. Platelets, 56,500 per c.mm. Fragility test: haemolysis started at 0·3 per cent. saline solution, i.e.

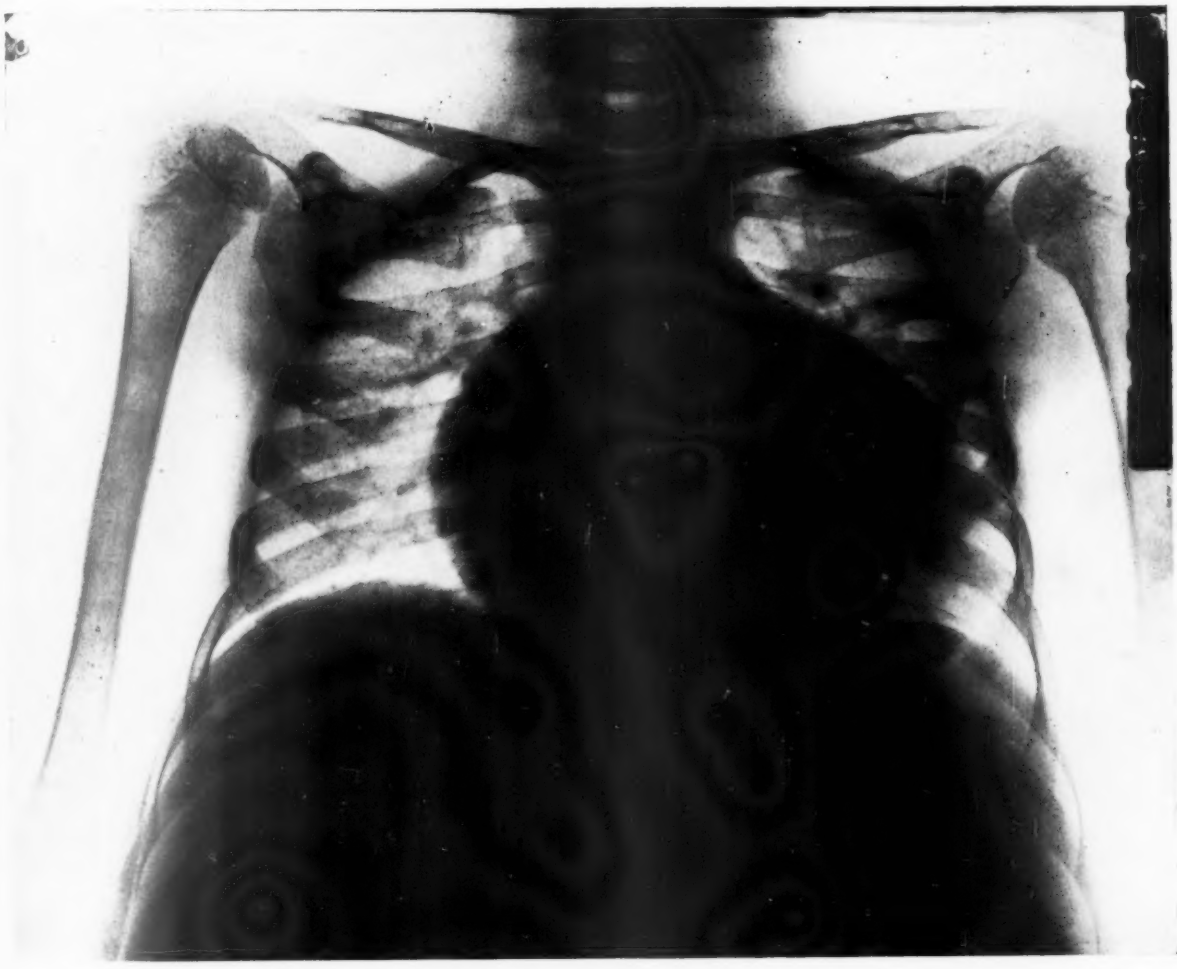

FIG. 8.—M. M. Note marked enlargement of heart, and osteoporosis of humerus, scapula, clavicle, and ribs.

increased resistance. Icterus index was 20 units; Van den Bergh gave an indirect positive result. Bleeding time was 4 minutes, coagulation time 4 minutes. Wassermann reaction negative. Blood film was negative for malaria. Stools were repeatedly negative for parasites. Bone marrow puncture revealed a definite erythroblastic reaction going to hypoplasia.

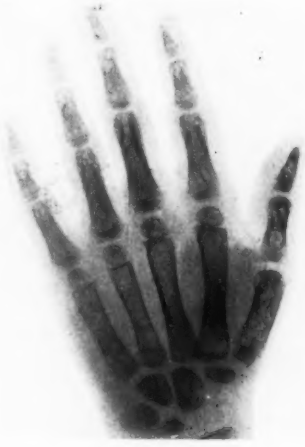

FIG. 9—Case 3. See text.

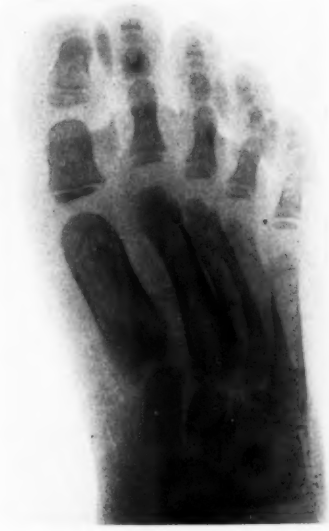

FIG. 10.—Case 3. See text.

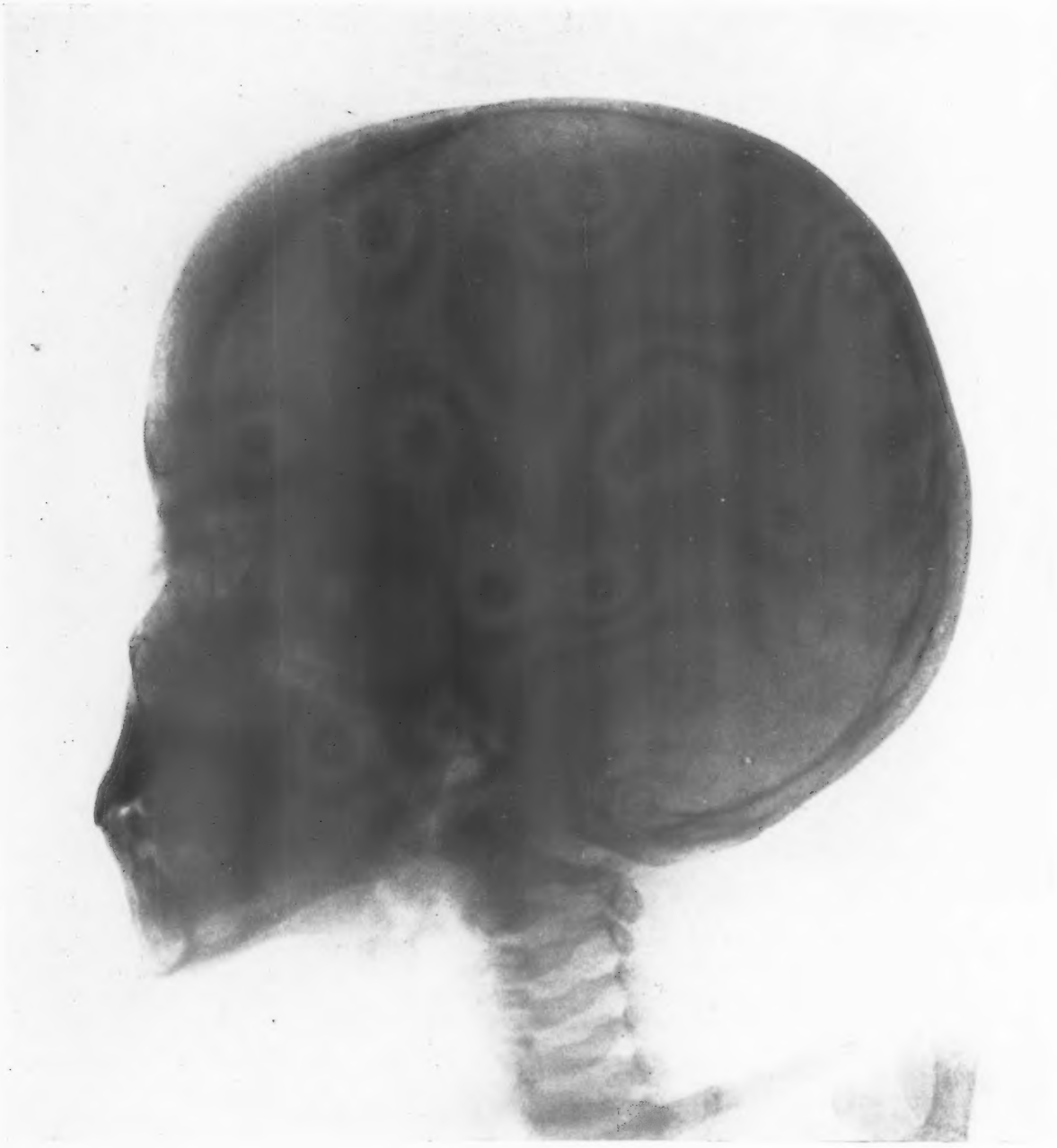

FIG. 11.—Case 3. See text.

X-ray examination of bones showed marked generalized osteoporosis, and the skull showed typical 'hair on end' appearance. The heart showed enlargement of all chambers (fig. 8, 9, 10, 11).

## Summary

1. Three cases of Cooley's syndrome are described. Two of them occurred in genuine Egyptian children, the third in a Greek child.

2. Sternal marrow biopsy done in two of the cases revealed a marked erythroblastic hyperplasia.

3. Marked enlargement of the heart was noticed in two of the cases.

Thanks are due to Dr. A. Omar and Dr. M. Nabawy for their kind help and co-operation.

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# OBSERVATIONS ON THE URINE OF THE NEW-BORN INFANT

BY

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Publications dealing with the physical and chemical characteristics of the urine in the new-born period date from 1864. They are most common in the German literature of last century. In some instances the observations are incomplete while in others they are obviously inaccurate. In general, these shortcomings arise from the difficulty of collecting the specimens of urine. Many ingenious methods of collecting urine from infants and young children are on record and a close search of the literature reveals over forty references to the subject. The apparatus in use in the present investigation consists of two parts, the one a urinal and the other an electrical signalling device.

### Apparatus

The urinal is made from the following materials:

(1) A rubber pear-shaped ear syringe
(2) A white collar stud
(3) A piece of rubber tubing
(4) A collecting vessel with a two-holed rubber stopper
(5) A pair of rubber straps about 11 inches long by ¾ inch broad
    These can be cut from a disused motor-car inner tube
(6) Safety pins

Fig. 1, 2 and 3 show the construction and method of application of the urinal. The aperture in the side of the syringe is not more than 1¼ inches in diameter. The collar stud passes through the wall of the syringe from within outwards and directly opposite the aperture. It then passes through the centre of each of the rubber straps in turn. It is essential to fit the appliance carefully. For this purpose it is necessary to have about six syringes available. Each syringe has a slightly different size of aperture. In the case of the male infant the scrotum and penis are slipped inside the syringe while in the case of the female infant the aperture in the syringe encloses the labia majora. It is necessary to pin the rubber straps up with sufficient tension to prevent the syringe from falling away from the external genitalia. Care must also be taken not to pull the syringe backwards over the anus. A rubber tube is attached to the exit from the syringe and leads to a collecting vessel. A test-tube, held vertically in a retort stand at the cot side, is satisfactory.

The electrical signalling device consists of a glass float chamber and an ebonite stopper which carries two electrical terminals. The method of construction and operation are clearly shown in fig. 4. The electrical circuit closes when the float rises, and opens when the float chamber is drained.

### The daily volume of urine

It is recognized that the daily volume of urine which the infant passes during the first days of life varies greatly and that there is a considerable variation from infant to infant. Fig. 5 illustrates

FIG. 1.—Selecting a syringe of a suitable size.

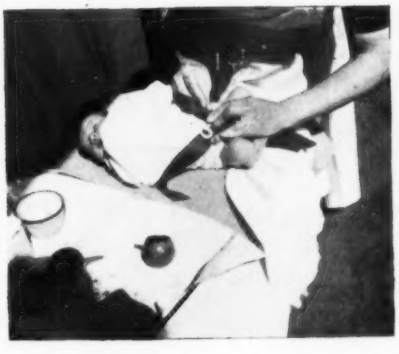

FIG. 2.—Fastening the anterior ends of the rubber straps.

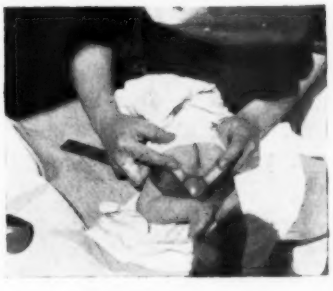

FIG. 3.—To show clearance from the anus.

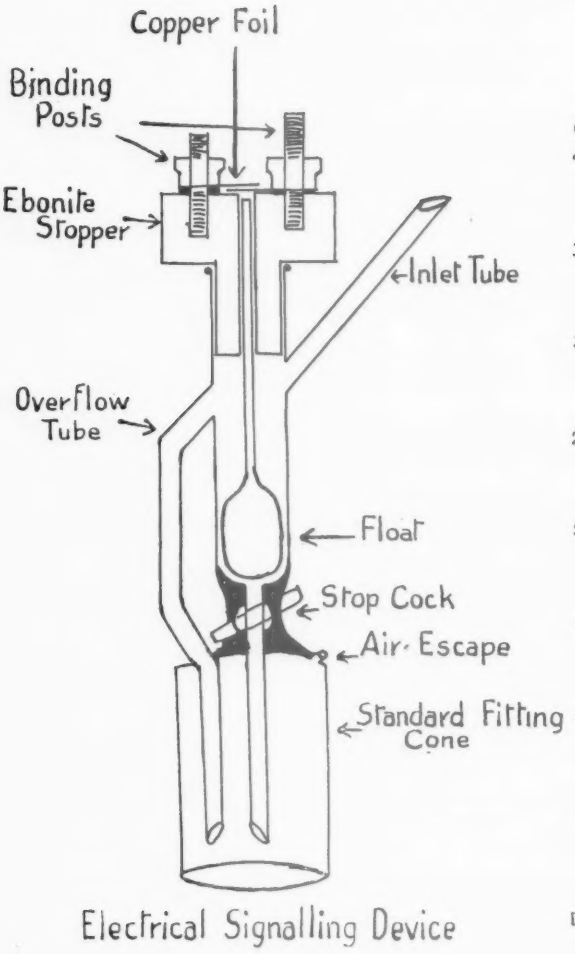


FIG. 4.

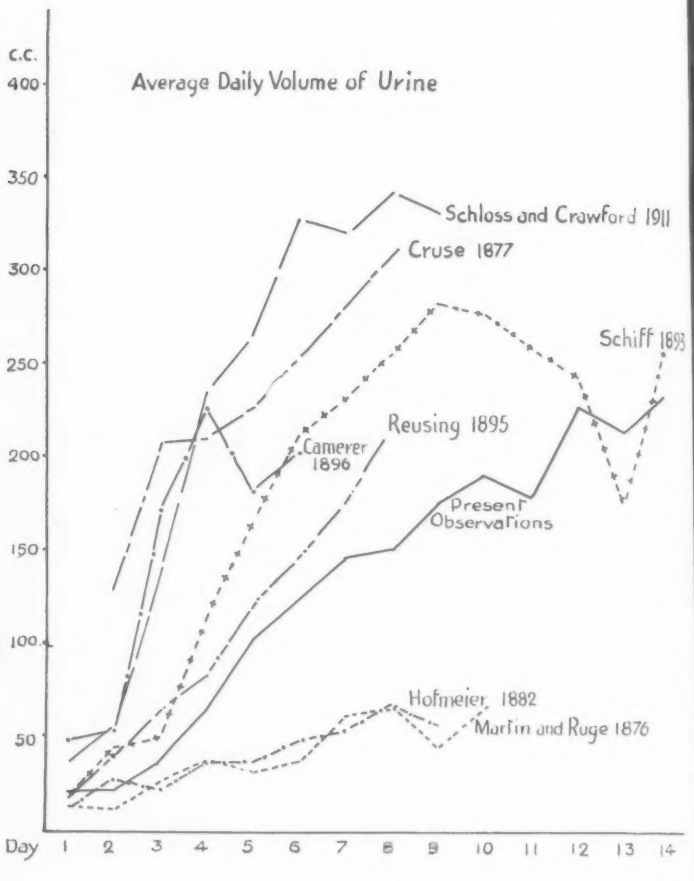


FIG. 5.

the average daily amount which is passed by the new-born infant. It shows, as might be expected, a steady increase from day to day. This is in sharp contrast to the findings of Martin and Ruge (1876), and Hofmeier (1882). In both these cases the figures given are almost certainly inaccurate from the fourth day onwards. The publications of Cruse (1877) and Camerer (1896) record figures considerably greater than those now published. It is clear that this is due to abnormally large intakes of fluid for Cruse states that the infants were foundlings and that they were put to the breast of wet nurses who had already been lactating for an average period of four-and-a-half months. Though no information is given on this point, a similar explanation probably accounts for the high figures of Schloss and Crawford (1911). The graph now published approximates to that which represents the observations of Reusing (1895), while at its beginning and termination it shows a certain similarity to that representing the work of Schiff (1893). Unfortunately, Schiff gives no information concerning the daily volume of the intake.

Whilst the graph illustrates a steady rise in the average daily volume of the urine, table 1 shows a wide range within which the daily volume of the urine may vary. These daily variations are well illustrated by the following three cases.

| Day | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| No. 3418. G. c.c. | 10 | 5 | 22 | 27 | 26 |
| No. 7402. T. c.c. | nil. | 8 | 16 | 50 | 77 |
| No. 7655. M. c.c. | 21 | 32·5 | 7 | 31 | 44 |

| Day | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|
| No. 3418. G. c.c. | 47 | 97 | 112 | 92 | 195 |
| No. 7402. T. c.c. | 57 | 81 | 82 | 244 | — |
| No. 7655. M. c.c. | 83 | 71 | — | — | — |

It is certain that at this age period, as at all others, the most important factor to determine the volume of the urinary output is the amount of the fluid intake. Table 2 gives the average volumes of the

TABLE 1

AVERAGE DAILY VOLUME OF URINE

| Day | Volume, c.c. | Range, c.c. | Number of infants |
|---|---|---|---|
| 1 .. .. | 19·5 | 0– 68 | 35 |
| 2 .. .. | 20·6 | 0– 82 | 29 |
| 3 .. .. | 36·0 | 0– 96 | 26 |
| 4 .. .. | 64·8 | 5–180 | 26 |
| 5 .. .. | 103·3 | 1–217 | 23 |
| 6 .. .. | 124·5 | 42–268 | 19 |
| 7 .. .. | 146·6 | 40–302 | 18 |
| 8 .. .. | 151·0 | 59–330 | 17 |
| 9 .. .. | 175·4 | 57–355 | 14 |
| 10 .. .. | 190·0 | 106–320 | 6 |
| 11 . .. | 179·0 | 120–217 | 3 |
| 12 .. .. | 227·0 | 207–246 | 2 |

TABLE 2

AVERAGE DAILY INTAKE AND OUTPUT

| Day | Number of infants | Milk, c.c. | Urine, c.c. | Per cent. of intake returned as output |
|---|---|---|---|---|
| 1 .. | 27 | 28·3 | 21 | 74·0 |
| 2 .. | 26 | 67·0 | 22 | 46·5 |
| 3 .. | 26 | 146·9 | 37 | 25·0 |
| 4 .. | 25 | 243·2 | 62 | 25·5 |
| 5 .. | 23 | 311·5 | 99 | 31·7 |
| 6 .. | 20 | 364·0 | 115 | 31·6 |
| 7 .. | 21 | 364·8 | 144 | 39·5 |
| 8 .. | 19 | 382·5 | 142 | 37·1 |
| 9 .. | 13 | 412·5 | 162 | 39·2 |
| 10 .. | 6 | 387·5 | 190 | 49·0 |
| 11 .. | 3 | 410·0 | 179 | 43·8 |
| 12 .. | 2 | 382·5 | 227 | 59·3 |

intake and the output recorded in this investigation. The percentage of the intake returned as urine is also shown. Data of this nature are also published by Reusing, table 3. It is not possible to draw any conclusions from a comparison of the two tables for several reasons. The number of the infants varies during the period of observation in table 2. There are statistical inaccuracies on the first and seventh days in table 3, and in addition an error in the calculation of the percentage on the seventh day. Apart from his inaccurate use of figures, Reusing's data include infants whose daily water balances are negative or nearly so. For example, one of the six infants has negative water balances of 72 c.c., 41 c.c. and 61 c.c. on the fifth, sixth and seventh days of life respectively. Because of this it is reasonable to doubt whether Reusing's figures can be looked upon as being representative of average normal infants. Nevertheless, Reusing's data have been freely quoted in the paediatric literature.

TABLE 3

AVERAGE DAILY INTAKE AND OUTPUT (REUSING)

| Day | Number of infants | Milk, c.c. | Number of infants | Urine, c.c. | Per cent. of intake returned as output |
|---|---|---|---|---|---|
| 1 .. | 3 | 38·3 | 6 | 8·4 | 21·8 |
| 2 .. | 6 | 120·8 | 6 | 26·8 | 22·2 |
| 3 .. | 6 | 176·6 | 6 | 40·9 | 23·1 |
| 4 .. | 6 | 220·0 | 6 | 60·8 | 27·6 |
| 5 .. | 6 | 271·5 | 6 | 119·2 | 43·9 |
| 6 .. | 6 | 296·6 | 6 | 148·6 | 50·0 |
| 7 .. | 6 | 297·0 | 5 | 157·0 | 57·6 |
| 8 .. | 6 | 333·0 | 6 | 208·0 | 62·5 |

### The frequency of micturition

Fig. 6 illustrates the data collected by means of the electrical signalling device. Martin and Ruge are the only other investigators to publish similar observations. Their data are also shown. The

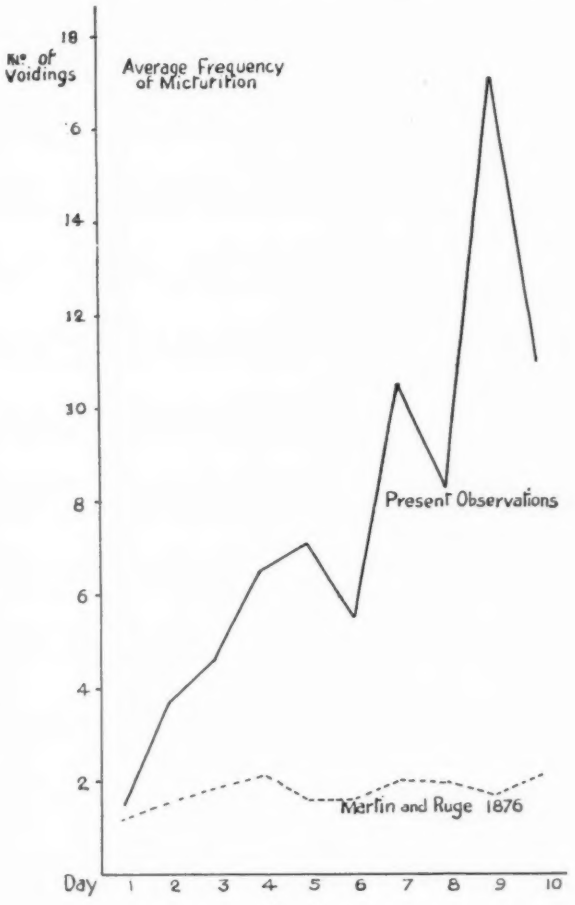


FIG. 6.

divergence between the two series of observations is so great that there is no possibility of reconciling them. It is reasonable to expect that the frequency of micturition should increase with the gradual increase from day to day in the intake of fluid. Engel (1914) has shown that in older infants an increased intake means an increased frequency of micturition. That the new-born infant is no exception to the rule is demonstrated by case No. 7402.

| Day .. .. | 7 | 8 | 9 | |
|---|---|---|---|---|
| Intake .. .. | 232·5 | 277·5 | 450·0 | c.c. |
| Output .. .. | 81 | 82 | 244·0 | c.c. |
| Average volume of single specimens .. | 10·12 | 11·71 | 9·76 | c.c. |
| Frequency .. .. | 8 | 7 | 25 | times |

The data given by Martin and Ruge are based partly on direct observation of micturition, and partly on inference. This, no doubt, is the explanation of the discrepancy disclosed by the graph.

### The volume of urine passed at one voiding

The amount of urine passed at each voiding varies within wide limits. This is shown in table 4. The scatter of the observations is illustrated in fig. 7.

TABLE 4

| Day .. .. | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Maximum vol., c.c. .. | 30·0 | 34·0 | 34·0 | 38·0 | 32·0 |
| Minimum vol., c.c. .. | 1·5 | 1·0 | 2·0 | 3·5 | 2·0 |
| Average vol., c.c. .. | 9·2 | 10·2 | 12·5 | 13·5 | 11·7 |

TABLE 4—*continued*

| Day | 6 | 7 | 8 | 9 |
|---|---|---|---|---|
| Maximum vol., c.c. | 45·0 | 60·0 | 52·5 | 66·0 |
| Minimum vol., c.c. | 2·0 | 1·5 | 3·0 | 1·0 |
| Average vol., c.c. | 23·0 | 13·5 | 23·5 | 9·5 |

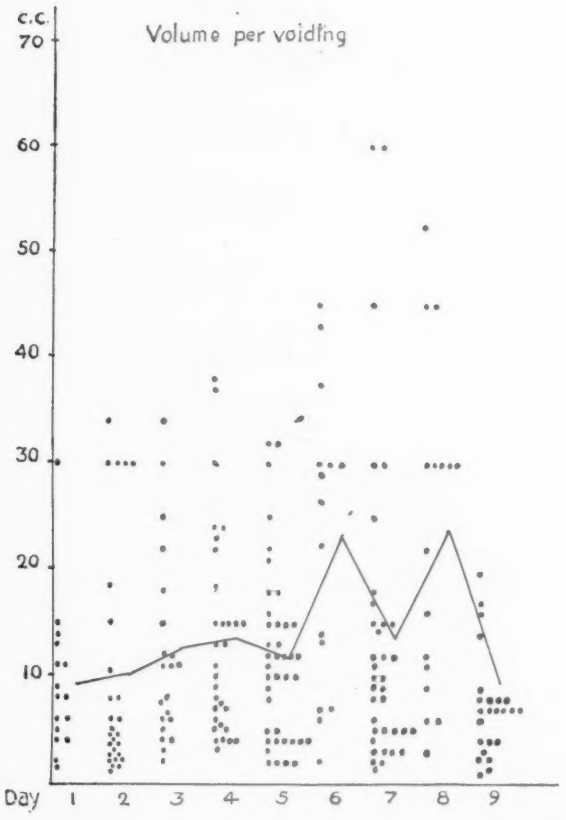


FIG. 7.

The average figure of 9·2 c.c. for the first day of life compares very favourably with the figure of 9·6 c.c. given by Martin and Ruge as the average volume of the first specimen of urine to be passed post-natally. Comparison is also not unfavourable with the figures of Dohrn (1867), Reusing (1895), Martin, Ruge and Biedermann (1875), and Parrot and Robin (1876). See table 5.

After the first five days the figures tend to become more erratic. This may be due to the observations being made on too small a number of infants and also to the greatly varying factor introduced at this time by the establishment of lactation. The wide range between the minimum and maximum volumes of urine passed at one voiding may be observed in one infant.

Example: Infant No. 9749. 2nd Day.

| Time | Urine, c.c. | Time | Urine, c.c. |
|---|---|---|---|
| 4.0 a.m. | 30 | 1.15 p.m. | 34 |
| 7.10 ,, | 7·5 | 4.0 ,, | 26 |
| 9.30 ,, | 30 | 4.30 ,, | 12 |
| 11.35 ,, | 1 | | |

Once lactation is fully established and the intake is sufficient to meet normal physiological requirements, the volume of urine passed at one voiding may be larger.

TABLE 5

VOLUME OF URINE PER VOIDING

| | | |
|---|---|---|
| Volume of urine in bladder post-natally | Dohrn 7·55 c.c. | Reusing 8·2 c.c. |
| Volume of urine at first voiding post-natally | Martin, Ruge and Biedermann 8 c.c. | Martin and Ruge 9·6 c.c. |
| Average volume of urine per voiding | Parrot and Robin | Present Observations |
| Day 1 | 5–10 c.c. | 9·2 c.c. |
| 2 | | 10·2 ,, |
| 3 | | 12·5 ,, |
| 4 | | 13·5 ,, |
| 5 | 10–25 c.c. | 11·75 ,, |
| 6 | | 23·0 ,, |
| 7 | | 13·5 ,, |
| 8 | | 23·5 ,, |
| 9 | | 9·5 ,, |
| 10 | 15–30 c.c. | |
| 11 | | |
| 12 | | |
| 13 | | |
| 14 | | |
| 15 | | |

Example: Infant No. 389. 6th Day.

| Time | Urine, c.c. | Time | Urine, c.c. |
|---|---|---|---|
| 4.0 p.m. | 45 M | 1.0 a.m. | 30 A |
| 7.50 ,, | 30 A | 8.30 ,, | 22·5 M |
| 11.0 ,, | 30 A | 11.0 ,, | 37.5 A |

Incidentally, this record shows how an attempt can be made to check the efficiency of the signalling apparatus and also to some extent estimate the capacity of the bladder. Observations marked A were made with the electrical apparatus, whereas those marked M denote the volume of urine passed at a nursing period when the infant was in its mother's arms. On these occasions the electrical apparatus is disconnected and is replaced by a test-tube. These high and relatively infrequent passages of urine are not to be looked upon as invariable. They may be contrasted with the following case.

Example: Infant No. 7675. 5th Day.

| Time | Urine, c.c. | Time | Urine, c.c. |
|---|---|---|---|
| 2.30 p.m. | 8 & 9 | 2.20 a.m. | 10 |
| 4.0 ,, | 4 | 3.15 ,, | 12 |
| 5.45 ,, | 13 | 4.0 ,, | 10 |
| 7.45 ,, | 12 | 7.30 ,, | 18 |
| 9.0 ,, | 12 | 8.20 ,, | 12 |
| 10.15 ,, | 13 | 11.20 ,, | 32 |
| 1.0 a.m. | 15 | 11.45 ,, | 10 |
| 1.30 ,, | 4 | 1.45 p.m. | 10 |

Broadly speaking, the data show a slow and gradual rise in the volume of urine voided on each occasion as the days pass, but a much more rapid rise in the frequency of micturition.

### The specific gravity

Owing to the smallness of the volumes of the urine it is not always possible to determine the specific gravity by the urinometer. Alternative methods are, either to use a Sprengle's tube or to follow the method of Kirkpatrick and Kling (1926). The present observations were made with a urino-

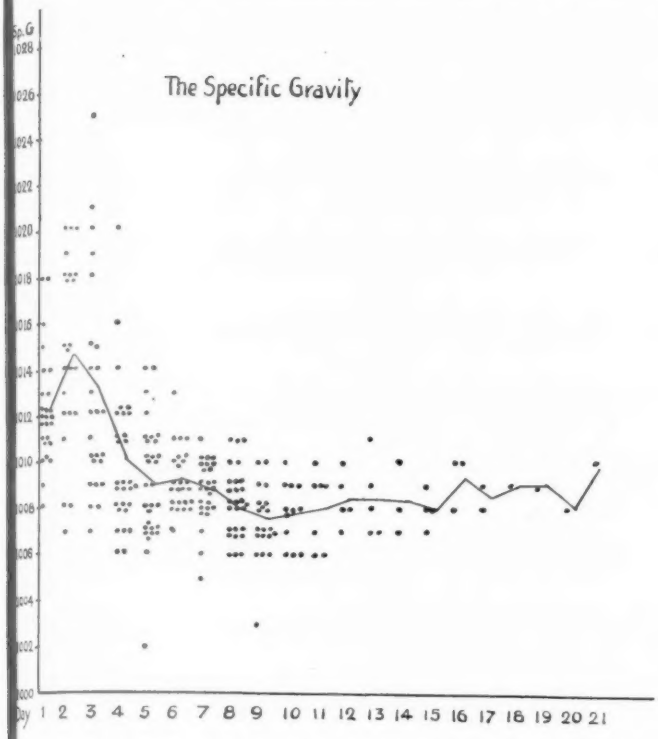


FIG. 8.

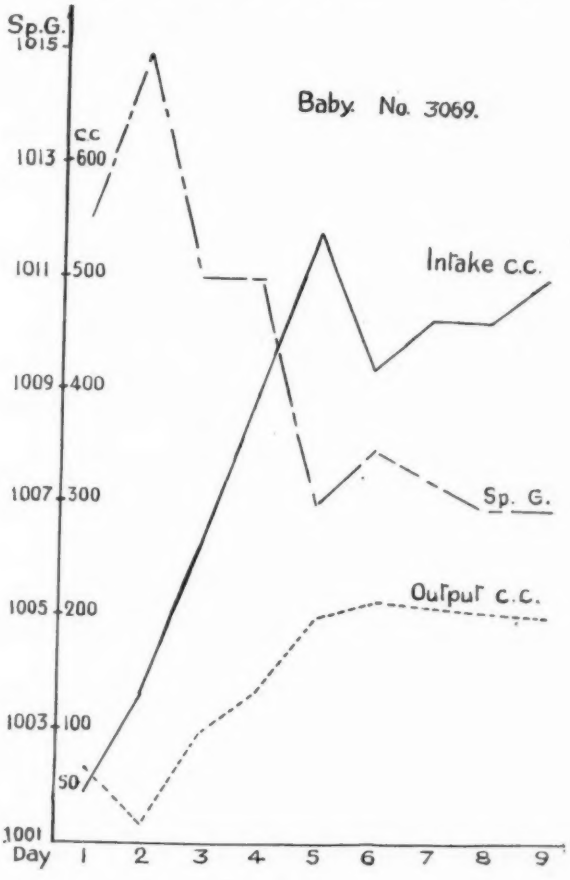


FIG. 10.

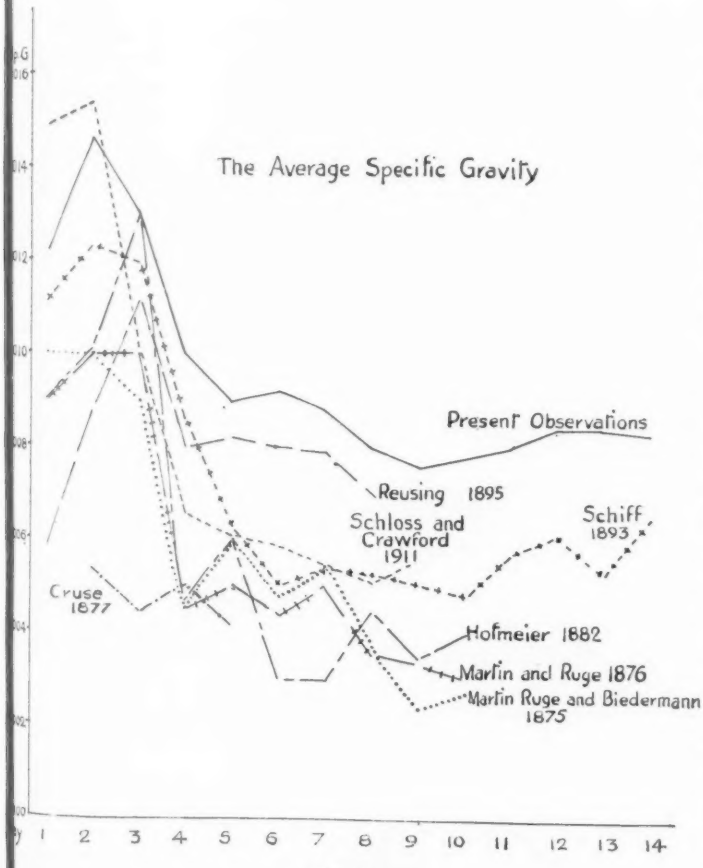


FIG. 9.

meter when possible and by direct weighing of the small specimens. The use of the urinometer to take the specific gravity of a specimen consisting of the pooled but varying volumes passed by different infants on the same day of life was practiced by Martin and Ruge (1876), Michel and Budin (1897), and Moore (1917). This method cannot give an accurate result. Schiff and Reusing were unable to give the specific gravity of all their specimens of urine because they relied on the urinometer.

The data obtained in the present investigation are shown in fig. 8. Following an initial rise in the first and second days there is a steady decline until the eighth day, when the specific gravity becomes more stabilized. This coincides with the time when the daily intake at the breast becomes more stable. The form of the graph is similar though not identical with that of Schloss and Crawford, Schiff, Hofmeier, Martin and Ruge, Martin, Ruge and Biedermann, and Reusing (fig. 9). The maximum figure reached is 1025 on the third day. This increase in the specific gravity of the urine during the first forty-eight hours of life is probably related to the infant's need to conserve the body water reserve during this period. The relationship between the increasing intake and the increasing output on the one hand and the fall in the specific

gravity of the urine on the other is well demonstrated in fig. 10.

### The *p*H of the urine

In estimating the hydrogen ion concentration of the urine the B.D.H. capillator method was used and the specimens were collected under a layer of toluol. The data collected are presented in fig. 11. It is observed that the daily average *p*H of the urine passes steadily from a very definitely acid concentration towards neutrality. This trend is not confined to the daily average figure but is observed in individual infants as the following examples demonstrate.

| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| No. 2840 .. | — | 5·8 | 6·2 | 6·7 | 6·7 | 7·0 | 7·0 | 6·8 |
| ,, 7400 .. | 5·6 | 6·0 | 6·2 | 6·6 | 6·8 | — | — | — |
| ,, 7655 .. | 5·8 | 6·0 | 6·6 | 6·5 | 6·5 | 6·6 | 6·4 | 6·8 |
| ,, 3054 .. | 5·5 | 5·8 | 6·2 | 6·0 | 6·0 | 6·0 | 6·6 | 6·7 |
| ,, 7402 .. | — | 6·0 | 6·0 | 6·3 | 6·4 | 7·0 | 7·3 | 7·0 |

The high *p*H observations made on the urine passed in the first few days of life are probably related to the acidotic state of the new-born infant (Seham, 1919). This is a matter of some clinical importance. It is well recognized that the new-born infant has an imperfectly developed defence mechanism against bacterial invasions. Unlike the adult it is peculiarly liable to succumb to a B. coli infection. The risk of a urinary infection is contributed to in some measure by the fact that the optimum *p*H for the growth of B. coli lies between *p*H 6 and *p*H 7 (Wilson, 1929). The high *p*H of the urine in the first two days of life is associated with a relatively low fluid intake, and therefore it is to some extent due to the need to conserve the body water reserve at this time. It is probable that here is an indication that it is desirable to supply the new-born infant with sterile water.

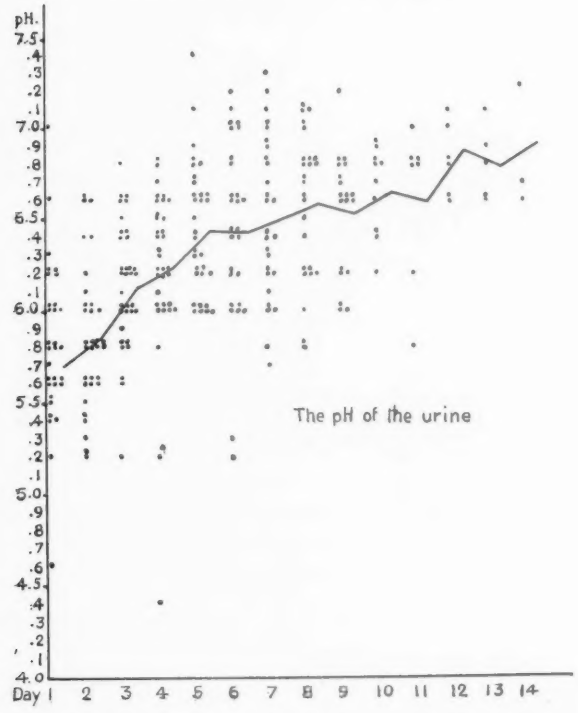


FIG. 11.

### The chloride content

There are few publications which deal with the chloride content of the urine in the new-born period. Picard (1856) is the earliest investigator and he is followed by Hecker (1857). Their work, like that of Parrot and Robin (1876) and Martin and Ruge (1876), is of no more than historic value. The data published by Cruse (1877) are not applicable to the average new-born infant since his observations were made on infants which were wet nursed. The only other publication is that of Schiff (1893).

The present investigation shows that there is a steady fall in the concentration of chloride during the first four days after birth. This is followed by an increase in the concentration during the next three or four days, after which a steady decline is again apparent. Fig. 12 shows that Schiff's data are very similar. The increase in the concentration of the chlorides from the fifth to the eighth days is, in all probability, due to more than one factor. An examination of the chloride concentration of colostrum and early breast milk shows that there is a steady decline from the first day onwards. This is shown in fig. 13. Nevertheless, the total chloride output increases steadily from the fourth to the

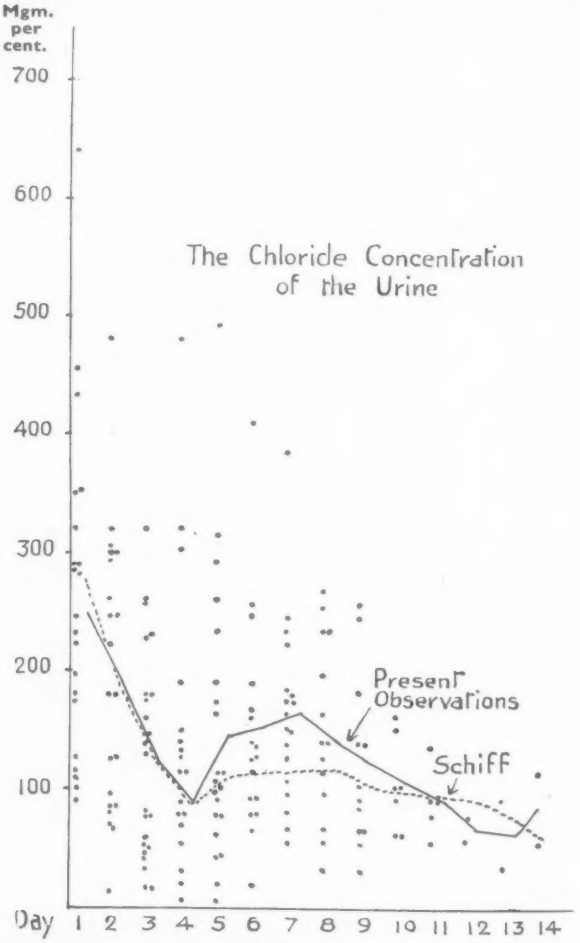


FIG. 12.

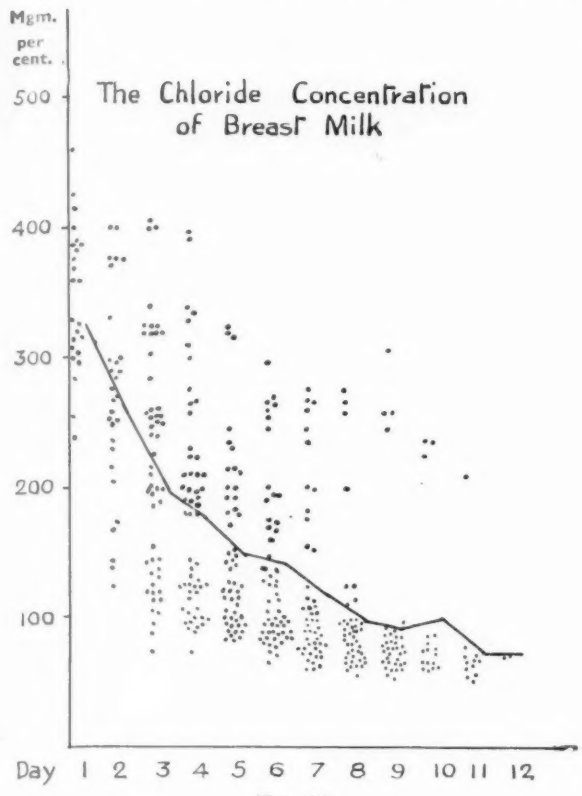


FIG. 13.

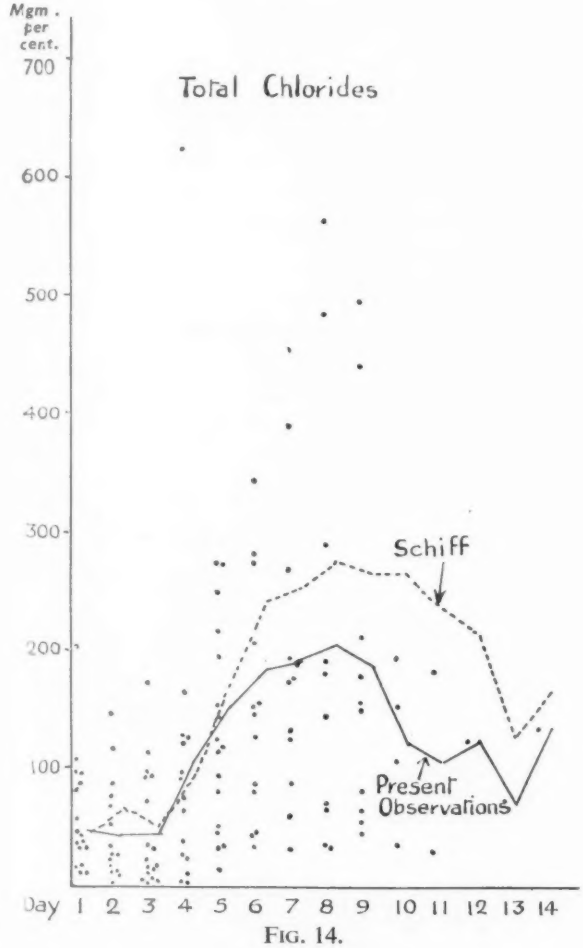


FIG. 14.

ninth day, a consequence no doubt, of the larger feeds obtained at the breast. During the first three or four days of life it is certain that there is a considerable depletion of the body water reserve and that this reserve is re-established at the earliest opportunity. It is probable that this is the explanation of the increase of the chloride concentration from the fifth to the eighth days, and its subsequent decline.

Here let it be said that publications dealing with the chloride content of colostrum and early breast milk are rare and there is no authoritative work published on chloride utilization by the new-born infant. The total daily chloride output varies considerably from infant to infant. It is probable that the time of the onset of lactation and the volume of the intake at the breast are the most important determining factors. These are variable. The total daily chloride output is shown in fig. 14. The graph is similar to but not identical with that representing the work of Schiff.

**The urea content**

Like all other observations on the urine in the new-born period the urea concentration varies widely, and especially so during the first four or five days. This is illustrated in fig. 15. The graph shows an increase in the urea concentration from 689 mgm. to 827 mgm. per cent. in the first twenty-four hours. This is followed by a steady decline to 156 mgm. per cent. on the twelfth day. The graph is similar to though not identical with those representing the work of Schiff and Reusing (fig. 16). It is observed that the highest concentrations occur during the first five days. The low volume of the fluid intake during this period and the consequent need to conserve the body water reserve are no doubt adequate explanation of this. It is interesting to note, and it is not without significance, that a similar trend in the urea nitrogen concentration of the blood in the new-born infant is reported by Schultz and Pettibone (1915), Sedgwick and Ziegler (1920) and Lucas et alia (1921) (fig. 17).

The total urea output varies considerably throughout the whole period. Reference to fig. 18 shows a variation of as much as 400 mgm. in the first twenty-four hours. This range is exceeded on every subsequent day, the difference on the ninth day being over 700 mgm. There are many factors which will influence the total urea output in this age period. The protein content of the colostrum and early breast milk is itself an exceedingly variable factor, and without a fuller knowledge of the protein intake it is idle to speculate upon or discuss the subject. Ranges of output amounting to more than double the above figures are published by Schiff (1893) and Reusing (1895). The daily urea output is not only wide in its range, it may also vary greatly from day to day in the same infant. For example:—

| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| 7655. Urea, mgm. | 222·6 | 542·75 | 127·4 | 669·6 | 1170·4 | 854·9 | 333·7 |

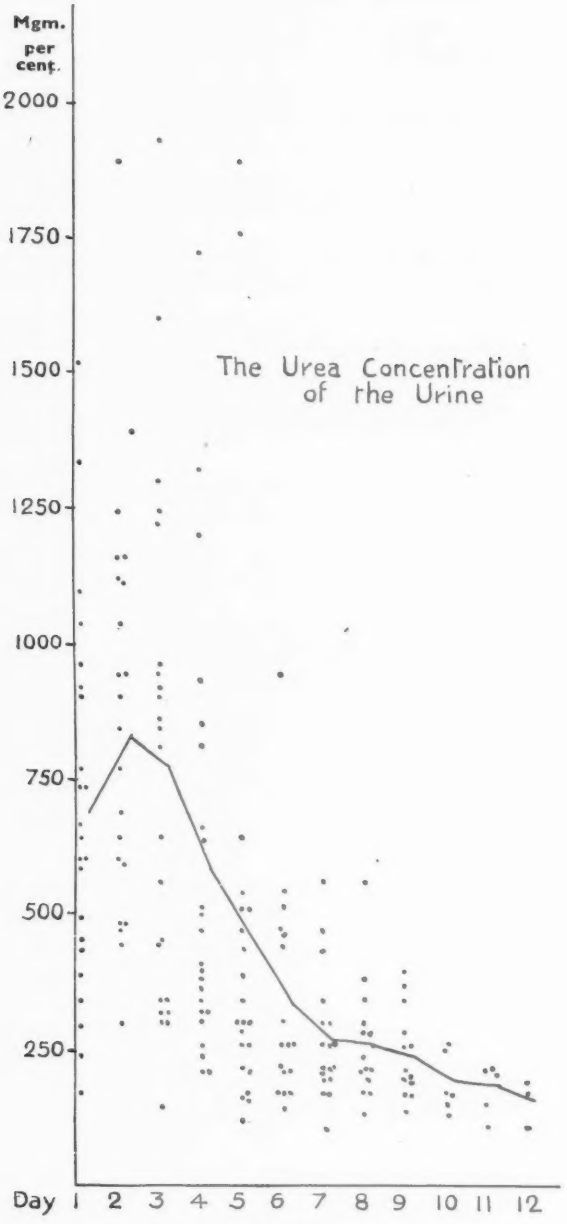


FIG. 15.

Similar variations are recorded by Schiff and Reusing.

### Commentary

These observations were made upon breast-fed infants of average weight and in whom there was no clinical evidence of abnormality. No case of dehydration fever is included. Neither is there any case of jaundice excepting a very transient physiological one. It follows that the results obtained are very much the reflection of the onset of lactation and the establishment of breast feeding. This physiological phenomenon varies greatly in different mothers and is not infrequently beset with many difficulties. Some of these are physiological in origin as, for example, excessive engorgement of the breasts; others arise from defects of structure, for instance, the retracted nipple. Yet others, like

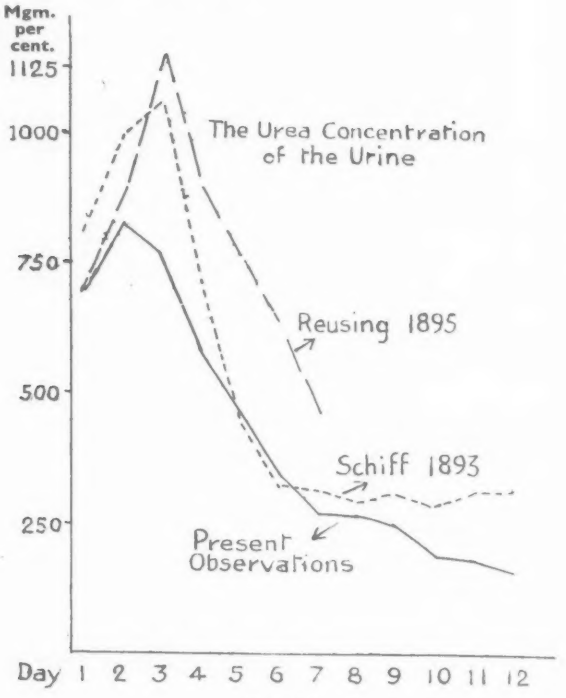


FIG. 16.

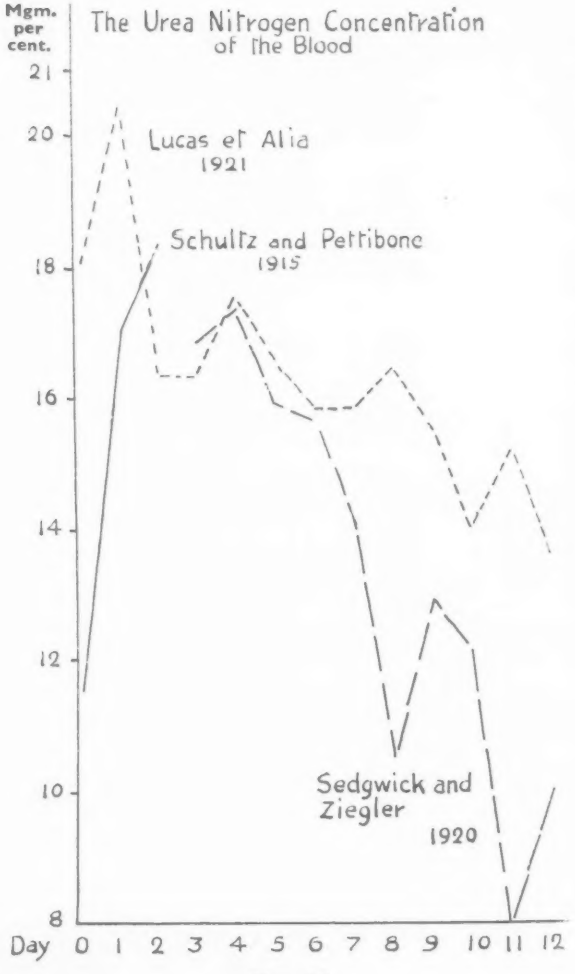


FIG. 17.

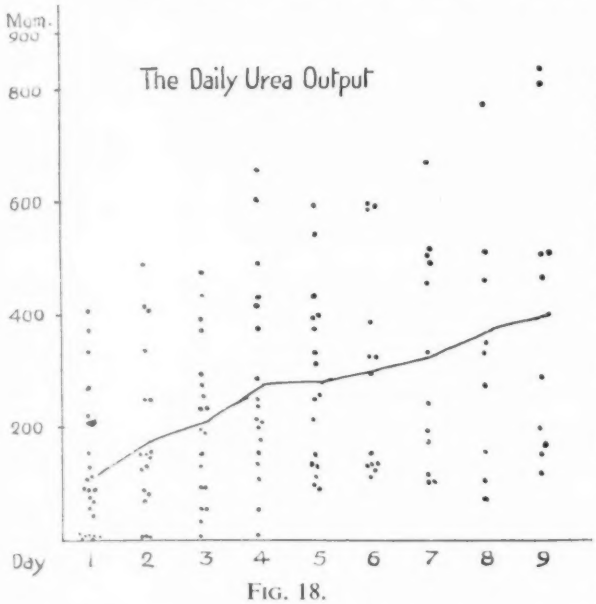


FIG. 18.

fissured nipples and mastitis, are frankly pathological. With such a capricious source of nutrition it is not to be wondered at that in some new-born infants there are wide fluctuations in the volume of the urine and the output of urea and chloride from day to day. Nevertheless, the results obtained show that in the first days of life the volume of the urine gradually increases as does the frequency of micturition. The output of urea rises each day, but no parallel course is seen in the chloride output. The specific gravity falls while the *p*H travels steadily towards alkalinity.

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# MYOCARDITIS IN ACUTE INFECTIVE DISEASES

## A REVIEW OF 200 CASES

BY

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The acute infective diseases constitute the most important cause of myocarditis, the commonest heart disease in childhood. Increasing amount of evidence from electrocardiographic investigations of the heart in acute infective diseases shows that there can be a myocarditis when clinical signs and symptoms are slight, doubtful or completely absent. These investigations further revealed that many convalescent cases whose unsatisfactory condition was accounted for by post-infective or secondary anaemia were actually suffering from myocarditis. Therefore, since this involvement of the myocardium is so common an event and liable to be missed or misdiagnosed, it seems justifiable to give an account of 200 cases of myocarditis occuring in acute infectious diseases.

**General signs**. The children do not complain of any pains ; sometimes there is abdominal discomfort. They do not resent examination and are not irritable.

**Clinical signs**. There is always some pallor and listlessness. Not infrequently vomiting occurs and may be the first sign. The urine often shows albuminuria, varying from the presence of a trace to a heavy deposit. The principal clinical signs are diminution in intensity of the first sound at the apex, indicating a weakness of the myocardium. The first sound becomes equal in intensity to the second apical sound, later on it becomes weaker and may even become entirely inaudible. Changes in the character of the cardiac rhythm take place, as shown by persistent tachycardia, less frequently bradycardia, embryocardia or gallop rhythm. Some degree of cardiac enlargement is common in severe cases of myocarditis. An important sign is a low blood pressure, the diastolic reading being often extremely low. The electrocardiogram is an important aid in the diagnosis of a myocarditis. The first sign is a flattened T wave; later on the T wave becomes isoelectric and eventually inverted. A second sign of myocarditis is an S–T segment below the isoelectric line in lead I and II or in both. It is conclusive evidence of a myocarditis when found together with a change in the T wave. A third sign of myocarditis is a diminution of voltage of the ventricular deflections to less than 1·5 mV voltage in all three limb leads together. This sign occurs especially in cases of severe myocarditis.

**Pathological anatomy**. Whenever possible the heart of a fatal case was examined in the Pathological Department (Prof. B. Shaw) of King's College, Newcastle upon Tyne. Two illustrative cases are given :

1. Sheila F., ten years, died on the eleventh day of diphtheria. Immediately beneath the ventricular endocardium and also in the inner third of the wall are some scattered small foci of lymphoid and histiocytic cells. These foci sometimes occur in association with shrunken muscle fibres and what appear to be small delicate recent scars.

2. Iris N., eight years old, died on the fourth day of diphtheria. Beneath the endocardium of the left ventricle there are a few patches of interstitial myocarditis in which the muscle fibres are disappearing and there is accumulation of mobile histiocytes and lymphocytes.

In the present series of 200 cases there are :

122 cases of diphtheria ;
10 cases of diphtheria in inoculated children ;
40 cases of scarlet fever ;
24 cases of whooping cough ; and
4 cases of measles.

The diagnosis of myocarditis was made on clinical grounds in 55 per cent. of the present series, by means of an electrocardiogram with doubtful clinical signs in 20 per cent. and on electrocardiographic findings with no clinical signs present in 24 per cent. The duration of the myocarditis in the present series was two to three weeks in 17 per cent., five to nine weeks in 58 per cent., three to four months in 25 per cent. The termination of the myocarditis was ascertained clinically in 13 per cent., clinically and by means of an electrocardiogram in 12 per cent., and by means of a graphic record alone in 75 per cent., when the clinical signs had subsided or they had not been present at all.

**Frequency of clinical signs (percentage)**

| | |
|---|---|
| Vomiting .. .. .. .. | 23 |
| Albuminuria .. .. .. .. | 38 |
| Enlargement of cardiac dullness .. | 21 |
| Heart sounds : | |
| 1=2nd apical sound .. .. | 15 |
| 2>1st apical sound .. .. .. | 29 |

Rhythm :

| | |
|---|---|
| Persistent tachycardia | 36 |
| Bradycardia | 17 |
| Embryocardia (tic-tac rhythm) | 9 |
| Gallop rhythm | 6 |
| Extrasytoles | 16 |

**Blood pressure (mm. Hg)**

| Age in years | Normal systolic | Normal diastolic | Lowest readings in present series systolic | Lowest readings in present series diastolic |
|---|---|---|---|---|
| 3 | 90–100 | 70 | 48 | 30 |
| 4 | 100–115 | 70 | 40 | 30 |
| 5–6 | 110–120 | 75–80 | 40 | 20 |
| 7–10 | 115–120 | 80–90 | 62 | 24 |
| 12–17 | 120–130 | 90 | 70 | 38 |

**Frequency of electrocardiographic signs. (Percentage)**

LIMB-LEADS

| | | |
|---|---|---|
| Changes of T wave : | | |
| T of less than 0·1 mV voltage, round | 47 | 54 |
| T isoelectric | 18 | |
| T inverted | 6 | |
| S–T segment below the base line | 27·5 | |
| QRS of less than 1·5 mV voltage in all three leads | 38 | |
| Extrasystoles | 12 | |
| Sinus tachycardia | 32 | |

CHEST-LEADS

| | | |
|---|---|---|
| QRS inverted | 64 | |
| Voltage of QRS less than 0·8 mV | 80 | |
| S-T segment depressed | 17 | |
| S-T segment below the base line | 6 | |
| Changes of the T wave: | | |
| T of less than 0·1 mV voltage | 17 | 86 |
| T inverted | 18 | |
| T isoelectric | 36 | |
| T diphasic | 5 | |

The changes of the T wave in the chest-leads enumerated above cannot be interpreted as a myocarditis if not combined with other alterations because they often occur in healthy infants and young children.

Once a myocarditis has been present there is the danger of its recurring in the course of another infective disease. Each of these subsequent attacks may cause further injury to the heart and may prove fatal. Actually it was found that in the majority of the 200 cases the patient had one, two or more acute infective diseases within the last year and in some instances up to five acute diseases within the last three years.

Incidence of preceding infective diseases in 200 cases of acute myocarditis (percentage).

| | |
|---|---|
| Measles | 25 |
| Measles and whooping cough | 22 |
| Measles and chickenpox | 9 |
| Whooping cough | 7 |
| Scarlet fever | 6 |
| Lobar and bronchopneumonia | 15 |

Death occurred in 4 per cent. of the present series. It is noteworthy that the fatal event occurred in two cases of diphtheria, where the history reported four infective diseases within three years (whooping cough, chickenpox, measles, scarlet fever) in one case and three diseases in another case.

**Diphtheria**

It would be superfluous to discuss in detail here the myocarditis in diphtheria. Vomiting, changes in the quality of the first apical sound, changes in the heart rhythm, and low blood pressure are clinically the most suggestive evidence of a myocarditis. Severe albuminuria early in the disease has always been regarded as a signum mali ominis. In severe cases not only the myocardium but also the conducting tissue is involved resulting in partial or complete heart block or intraventricular block. In the present series, however, only cases of pure myocarditis are represented. In 7 per cent. of the cases there was a slightly prolonged P–R interval. It is important to underline the occurrence of myocarditis in diphtheria in inoculated children. Severe complications are rare in diphtheria in the inoculated, but myocarditis does occur. General signs and symptoms, and clinical findings are the same as in the non-inoculated but occur in milder degrees and the electrocardiogram gives a good clue to the diagnosis ; involvement of the conducting tissue is rare in these cases.

**Scarlet fever**

Heart complications in scarlet fever occur towards the end of the second week, more frequently during the third week of disease and even later. The first symptom is pallor, the temperature is slightly raised for a few days or is normal. The pallor becomes more intense after a week or two and persists into late convalescence. The patient often loses weight. The cardiac dullness is enlarged, but only in severe cases is the dilatation extensive. The intensity of the first apical sound becomes less than that of the second and accompanying or following this change, a murmur develops. The development of murmurs is common in scarlet fever and it is important to distinguish functional murmurs from those caused by myocarditis or endocarditis or by both. Generally speaking myocarditis is more common than endocarditis in scarlet fever. Hence murmurs which occur in the course of scarlet fever have to be regarded as due to a diseased myocardium in the first place and to an endocarditis in the second place. There are three criteria of a carditis in scarlet fever : (1) The blood sedimentation rate is markedly increased as in rheumatic fever; (2) The electrocardiogram shows definite signs of a myocarditis and signs of a valvular disease, e.g. a mitral stenosis in some instances, later on ; (3) the x-ray examination reveals the enlargement of the heart. However, since the clinical signs are varied and poor at the onset, diagnosis might be difficult. The clinical and electrocardiographic signs are similar to those seen in rheumatic fever and last for several weeks or even months. When the myocarditis subsides the murmur disappears and the patient makes so complete a recovery that all evidence of the disease vanishes. Murmurs caused by valvular disease persist in the majority of cases. Per-

manent cardiac damage was observed in some of the cases recorded here.

### Whooping cough

Myocarditis is caused by two factors in whooping cough. One is merely mechanical : it is the strain put upon the heart by the severe paroxysms of cough during the third and fourth week of the disease. The second cause is the toxic effect of the infection on the heart-muscle. It is obvious that myocarditis is more often seen in cases of whooping cough complicated by bronchopneumonia. The pallor, lassitude, and tiredness of these patients is remarkable. The cardiac dullness is enlarged, especially to the right. Tachycardia is persistent and often of extreme degree. Blood pressure is lowered. The electrocardiogram shows right ventricular preponderance besides the typical signs of myocarditis and sinus-tachycardia. In many instances clinical and electrocardiographic signs might be found eight to twelve weeks after the whooping cough subsided. In cases of severe whooping cough, when there is anaemia or general weakness, listlessness and palpitation on exertion in late convalescence, which cannot be explained otherwise, the possibility of a myocarditis should always be considered.

### Measles

Heart disease in measles is rare. Indeed, when a myocarditis is encountered in an uncomplicated case of measles it is suspected to be a flare up of a myocarditis which originated in a preceding infectious disease. However, myocarditis is not uncommon in measles complicated with bronchopneumonia. The cases reported here are such cases. The general pattern of the myocarditis in measles is similar to that in all acute infectious diseases. It makes itself manifest during the febrile stage and subsides after the acute period.

### The convalescent child

A pale child with shadowed eyes, cold hands and feet, poor appetite and easily tired on exertion is often presented as the convalescent from an acute infective disease. Examination frequently yields few clinical findings or none at all, and since the blood picture is often one of an hypochromic anaemia, this anaemia is considered to explain the child's condition. It should be remembered, however, that anaemia is more often a sign of a disease than a disease in itself and that the partial examination of such a child—that is one which does not include an electrocardiogram—is more dangerous than no examination at all, because of the grave risk of the child being declared healthy when a myocarditis is actually present. This point cannot be stressed too often, an example of its practical importance is illustrated in a case such as the following :

A child, ten years old, inoculated against diphtheria, contracted 'tonsillitis.' As the child had suffered from tonsillar enlargement on a previous occasion, tonsillectomy was considered advisable. But since it made a slow recovery from its illness, being pale and easily tired, iron and other tonics were given to combat anaemia and strengthen the child. After five weeks of this treatment, the tonsillectomy was undertaken. About 60 minims of chloroform were given, followed by open ether : the pulse failed and the usual measures failed to bring the child round. Post-mortem examination revealed a myocarditis.

The protracted convalescence which may follow whooping cough has been mentioned before. It is interesting to see how an older generation of clinicians attacked this problem : they were fully aware that a child who exhibited the signs described above could not be regarded as healthy and recommended convalescence at the seaside or in the mountains, for several weeks. In this way, the patients did indeed procure the rest so essential as part of their treatment. If complete rest and good nursing be applied at once, the heart may be saved from irreparable damage. Some patients, it is true, do recover undiagnosed and untreated. Nevertheless, it is important that the correct diagnosis be made, because one key to the problem of lowering the incidence of heart disease lies in the early and correct diagnosis and adequate treatment of heart-complications of acute infective diseases in childhood.

Observations carried out over several years suggest that heart disease in adults might be due to repeated infections during childhood and adolescence, and that the lesions so produced often remain latent, so that clinically manifest heart disease does not appear until months and years afterwards.

Thanks are due to Dr. J. A. Charles, former medical officer of health, Newcastle upon Tyne, and to Dr. E. F. Dawson-Walker, medical superintendent of the Hospital for Infectious Diseases, Walkergate, for permission to carry out the investigation.

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# CASE REPORT

## GLYCOGEN STORAGE DISEASE

BY

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The diagnosis of glycogen storage, or von Gierke's disease, is frequently made only at autopsy, particularly if the clinical picture presents an unusual aspect of the disease. The most common clinical finding is enlargement of the liver associated with a low fasting blood sugar, a defective or absent rise in the blood sugar following an injection of adrenaline, and ketonuria. Many other features, however, have been described, and the clinical picture may be varied. This is not surprising in view of the underlying factor in the pathology of the disease, namely, that there is an excessive accumulation of glycogen, which is difficult of mobilization, in various organs. These organs vary from the liver, kidney, heart, intestines, stomach, pylorus and oesophagus, to the brain, spinal cord, blood vessels and striped muscles. It is because the present case shows unusual aspects of the disease that it seems worth while to report it.

The pathogenesis of the disease had not been finally settled. Ellis and Payne (1934) consider that the enzyme responsible for the breakdown of glycogen is missing within the liver cell. They also point out the possibility of anterior pituitary dysfunction as a cause, since Houssay and Biasotti (1931) have shown that extirpation of the pituitary results, among other things, in an increased resistance on the part of the liver to liberate glucose from its glycogen stores.

### Clinical record

P. M., male, aged three and a half months, was admitted to hospital on March 17, 1942, on account of feeding difficulties. He was the fifth child, full term, born by normal labour, and his birth weight was 6¾ lb. He was breast fed for the first three weeks, but he vomited occasionally, and failed to gain weight. He was then changed from cow's milk and water to national dried milk, and then to a proprietary full-cream dried milk, but without success, and the vomits which were at first regurgitations now ' shot out.'

On examination he was found to be wasted (weighing 6 lb. 1 oz.) and dark skinned. He was intelligent and took considerable notice of what was going on around him. The abdomen was prominent due to enlargement of the liver which extended 4 inches below the costal margin, and was firm and smooth, with a well defined edge. The spleen was not enlarged. There were no changes to be found in the central nervous system, or other systems.

**Progress.** Soon after admission the child had a ' fit.' He went a greyish-white colour, his respirations increased, there were slight generalized twitchings of his limbs, and he seemed exhausted. Nikethamide was given and he recovered shortly afterwards. In the following days he had several such attacks. During this time the child vomited occasionally but this was not projectile in character.

**Investigations.** Lumbar puncture showed no abnormality of the cerebro-spinal fluid.

A single blood sugar estimation was done two hours after a feed, and this showed 235 mgm. per cent. of sugar ; the urine on two occasions contained sugar in small quantities, on the first occasion no acetone was present, and on the second acetone was found.

The Wasserman reaction was negative.

The blood count showed a mild hypochromic anaemia, but was otherwise within normal limits.

On the assumption that this was an unusual case of diabetes mellitus, insulin was given, one unit half an hour before his feed. Half an hour after the insulin had been given, however, he had another attack similar to the previous ones, but recovered on being given his feed. He died the following day.

**Post-mortem findings** (less than twenty-four hours after death.) :

EXTERNAL—small wasted, male child.

BRAIN—slight congestion, otherwise normal.

CARDIOVASCULAR SYSTEM—heart muscle pale, but firm and of average thickness. Ductus arteriosus admitted a fine probe and foramen ovale slightly patent.

RESPIRATORY SYSTEM—a few areas of atelectasis in posterior parts of both lower lobes. Lungs slightly congested.

DIGESTIVE SYSTEM—tonsils, oesophagus, stomach, intestines, pancreas : nil abnormal. Liver : 10 oz., enlarged, smooth, pale yellow, fairly firm. Pattern : clear outline, with fine grey markings. Gall bladder etc. : normal. Light yellow bile.

HAEMATOPOIETIC SYSTEM—spleen : nil abnormal. Lymph glands : mesenteric slightly swollen.

URINARY SYSTEM—kidneys : slight congestion. Bladder : nil abnormal.

DUCTLESS GLANDS—nil abnormal.

**Microscopic examination**. Liver : sections of formalin-fixed material, stained with Best's carmine, show large quantities of glycogen in the liver cells abnormally resistant to post-mortem autolysis. There is a moderate increase of fibrous tissue producing the appearance of an early portal cirrhosis. A narrow rim of liver cells adjacent to the fibrous tissue at the periphery of the lobules contains less glycogen than the remainder of the lobules, but shows a slight degree of fatty change in addition (fig. 1).

HEART : myocardium of left ventricle contains a moderate amount of glycogen. The myocardial fibres do not appear enlarged. Glycogen cannot be demonstrated in the right ventricle but the fibres are somewhat vacuolated.

KIDNEYS : glycogen can only be demonstrated in an occasional cell of the renal tubules, but many of the tubular epithelial cells are pale and foamy and possibly may have contained this substance.

DUODENUM : a large amount of glycogen is demonstrable in the villi and mucosal glands.

## Discussion

The following are points of interest.

**Age.** It seems likely that glycogen storage disease is congenital since in patients described by Schall (1932), Unshelm (1931), and Kimmelsteil (1933), the large size of the abdomen was noted within the first few weeks of life, and those of van Creveld (1933), Bischoff (1932), and Holt (1932), probably from birth. In the majority of patients, however, symptoms are delayed until about three to five years, though the patient described by Holt was two days old at the onset, and the case here described had symptoms within the first few weeks of life.

**Vomiting.** This has been described by Worster-Drought (1923), Holmes á Court and Bray (1934), van Creveld and others, but has been cyclical in character. The significance of the presence of glycogen accumulation in the pylorus as a possible cause of pyloric stenosis in infants has been discussed by van Creveld.

Although none was found in the pylorus in the present case, the presence of glycogen in the duodenum may have been responsible for the projectile vomiting with which the infant suffered during the first few weeks of life.

**Hypoglycaemic attacks.** That the 'fits' were really attacks due to a lowered blood sugar seems probable since they occurred before meals, and were relieved by taking a feed. Hypoglycaemic attacks are surprisingly rare, having been described in only four cases up to the present.

## Other case reports

Holt describes the case of a female infant who developed respiratory distress two days after birth, and went into a state of collapse. Her liver was found to be greatly enlarged and there was acetone in her urine. The blood sugar level was 16 mgm. per cent. and she recovered on being given glucose saline infusion. There was no rise in the blood sugar level after an injection of adrenaline. She improved, and during the second month the glucose tolerance test showed a blood sugar level of 382 mgm. per cent at 1 hr., and 150, 121, 58 mgm. per

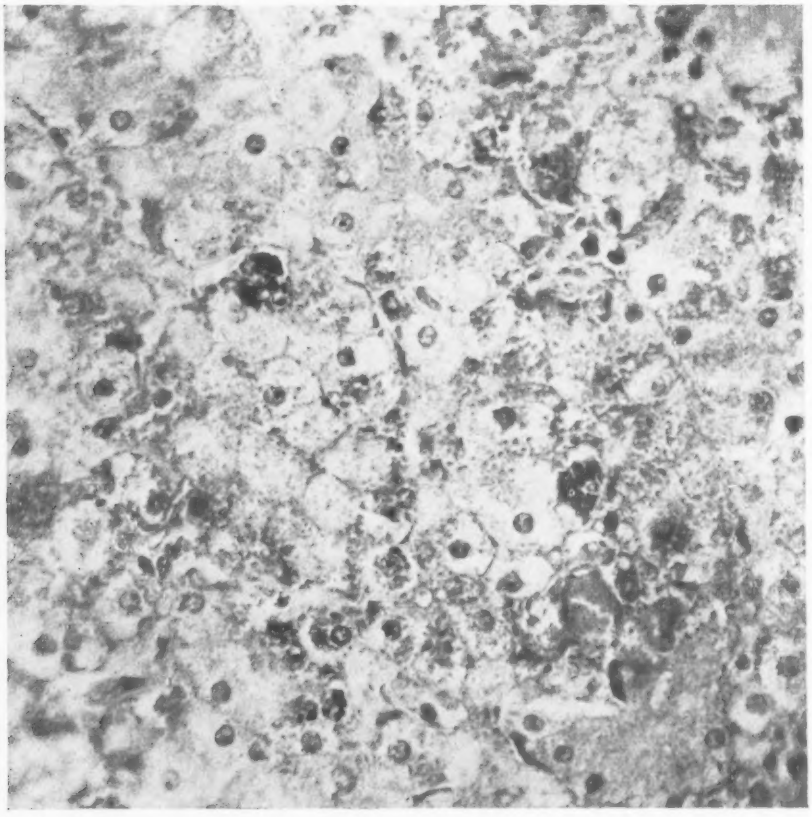

FIG. 1.

cent. at 2, 3, and 4 hours respectively. At the age of 2½ months she died of a respiratory infection, and autopsy showed a high percentage of abnormally stable glycogen in the liver.

Solomon and Anderson's (1933) case came under observation at the age of 22 months on account of failure to grow and gain weight. The liver was found to be enlarged, the blood sugar was within normal limits ; the urine contained a trace of sugar. Almost a year later the child began to have ' turns ' resembling epileptiform seizures, which always occurred between five and six in the morning. Acetone was found in the urine on one occasion. The fasting blood sugar was 56 mgm. per cent. and this rose to 88 mgm. per cent. after glucose ingestion. On feeding the child with an abundance of glucose at night the attacks did not occur.

Worster-Drought's patient came under observation at the age of ten years with a history of epileptiform attacks from one to four years. Then these attacks ceased, but she had been subject to attacks of cylical vomiting. On examination she was found to be undersized and had an enlarged liver. The fasting blood sugar was within normal limits, there was no glycosuria, but the urine contained acetone and diacetic acid.

Holmes á Court and Bray's case was first observed at the age of three and a half years, having had liver enlargement from the age of six months. She had a history of recurrent fits and attacks of vomiting since she was three months old, which had diminished in frequency. She was mentally retarded. The urine showed persistent acetonuria but no glycosuria. The fasting blood sugar was low, and the adrenaline response was negative.

**Summary**

The case report of a child aged three months suffering from glycogen storage disease is described: the main symptoms were projectile vomiting, and hypoglycaemic attacks.

Thanks are due to Dr. Wyllie for permission to publish this case and to Dr. D. M. Vaux for the post-mortem report and illustration.

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